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CURRENT CONCEPTS IN HYPOTHYROIDISM

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INTRODUCTION

HYPOTHYROIDISM is a disease which lends itself ideally to a multidisciplinary approach and to the use of a variety of techniques in an attempt to understand all of the complexities of this fascinating entity. The past fifteen years have seen the introduction of many new scientific techniques which have enabled one to delineate in a more precise manner the biochemical, physiologic, and metabolic abnormalities associated with failure of the thyroid gland to produce physiologic amounts of thyroid hormone.

It seems appropriate at this time to bring together in one volume some of the ideas of people working in this area of thyroid disease. The group from the Massachusetts General Hospital under Dr. John Stanbury's direction has made basic observations on the biochemical and enzymatic abnormalities present in certain goitrous cretins. Their review presents the current concepts of normal iodine metabolism and thyroid physiology and the defects which lead to the hypothyroid state. Dr. Sidney Ingbar heads a group of very active investigators at the Thorndike Laboratories primarily interested in the metabolism of thyroid hormones as related to protein binding. Their group was the first to show the binding of thyroid hormone to prealbumin (TBPA). This observation, plus many others which have helped to clarify many aspects of protein binding and thyroxin metabolism, has been critically evaluated for this review. Dr. Solomon Papper and his associates from the Medical College of Virginia, with a primary interest in fluid and electrolytes, bring us up to date on the abnormalities in this area which occur in hypothyroidism. The synthesis of new analogues of the thyroid hormones has created interest in cholesterol metabolism as influenced by these agents. Dr. Marvin Sachs of the University of Pennsylvania has critically reviewed the problem and formulates some new problems in this field which need further clarification.

Chronic thyroiditis—which ten years ago was a "pathologic curiosity"—has evolved as an exciting area for investigation from both the biochemical and immunologic standpoint. Dr. Charles Smart and his associates at Newcastle have been actively studying the problem and have reviewed their work plus that of others in an attempt to present the current concepts of this disease and its relationship to hypothyroidism.

Dr. John Wiswell of the University of Maryland reviews the present concepts of the diagnosis and treatment of both primary and secondary hypothyroidism. He has carefully evaluated the present laboratory tests available for diagnosis and the efficacy of the various thyroid hormones and their analogues used in treating the hypothyroid state.

Drs. Hamolsky, Kurland, and Freedburg of the Beth Israel Hospital in Boston have accumulated a large amount of data on the effect of induced hypothyroidism on the myocardium. Their review attempts to present some of the facts and controversies of this interesting complication. Drs. Nickel and Frame of the Henry Ford Hospital discuss myopathy and neuropathy, two complications of hypothyroidism which previously have not received the attention that is merited. Their review points out the fact that, if one is alert to these complications, "the incidence markedly increases."

Finally, Dr. William Jeffries of Western Reserve University reviews in detail the controversial problem of hypometabolism versus hypothyroidism. He has included a resumé of some of his interesting studies on the subject of "low thyroid reserve."

This series of papers obviously is not a complete review of the problem of hypothyroidism. Our aim was to compile some current thoughts on the subject which would provide the reader with a ready source of reference.

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THE METABOLISM OF IODINE IN THE THYROID GLAND

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THE demonstration in the early nineteenth century that burnt sponge and seaweed, used for centuries in the treatment of goiter, are rich in iodine resulted in the concept that the thyroid gland might be intimately concerned in the metabolism of that element. The beneficial effects of both iodine and thyroid in the treatment of goiter led Kocher to suggest in 1895 that the thyroid gland might itself contain iodine and, in the following year, its presence was demonstrated by Bauman. Intensive studies of the iodine-containing protein of the thyroid, thyroglobulin, culminated in the isolation of thyroxin by Kendall in 1915 and the subsequent determination of its structure by Harington.

Chromatography and the use of radioactive iodine have produced great advances in our knowledge of the nature of thyroid hormone synthesis. It has been clearly demonstrated that a series of reactions are involved, but as yet little is known about the actual mechanism of any of these steps. Verification of these various processes and of their importance for normal thyroid function have been obtained by the demonstration that genetically determined defects may occur at many stages[1] and result in the production of goitrous hypothyroidism and even of some cases of sporadic goiter.[2] It is indeed possible that many cases of so-called iodine-deficiency goiter have a mild underlying defect of a degree too slight to be revealed by present techniques and that this tendency to dyshormonogenesis, frequently familial, is merely unmasked by diminished availability of iodine. This may be a primary lack or may be produced by the ingestion of goitrogens.

Iodine enters the body either in the diet or medicinally; the average North American diet contains 100 to 200 μg of iodide per day. It may be ingested as ionic iodide in the reduced form, as iodine in the oxidized state, or as iodine in organic combination. Most forms of organic and elemental iodine are reduced to iodide during the processes of digestion and absorption and appear in the plasma as inorganic iodide. Absorption occurs largely in the small intestine. Iodinated

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thyronines and tyrosines may be transported intact across the gut wall, but the iodotyrosines are largely deiodinated prior to absorption. Certain iodinated aromatic compounds used in contrast roentgenography are also absorbed unchanged.

Iodide is present in the plasma in a concentration, except in the postabsorptive state, of less than 1 μg per 100 ml. It rapidly equilibrates through a diffusion space of approximately 28 per cent of body weight at 1 hour after ingestion. Although plasma iodide is excreted by the salivary and mammary glands, stomach, and part of the small intestine, most of it is either excreted by the kidney or trapped by the thyroid. These last two organs compete for the available iodide, and the rates at which they remove iodide from the plasma are therefore reciprocally related. The clearance rate of iodide by the kidney is relatively fixed, whereas that of the thyroid is adjusted to the iodide available and the physiologic activity of the gland. Losses of inorganic iodide in feces, sweat, and expired air are small.

A general scheme of iodide metabolism is illustrated in Fig. 1. The structural formulas of the biologically important iodinated compounds are shown in Fig. 2. Other iodinated compounds, 3,3′-diiodothyronine, and 3,3′,5′-triiodothyronine, as well as iodinated histidine, have been identified in thyroid tissue. Their biologic significance is not yet clear.

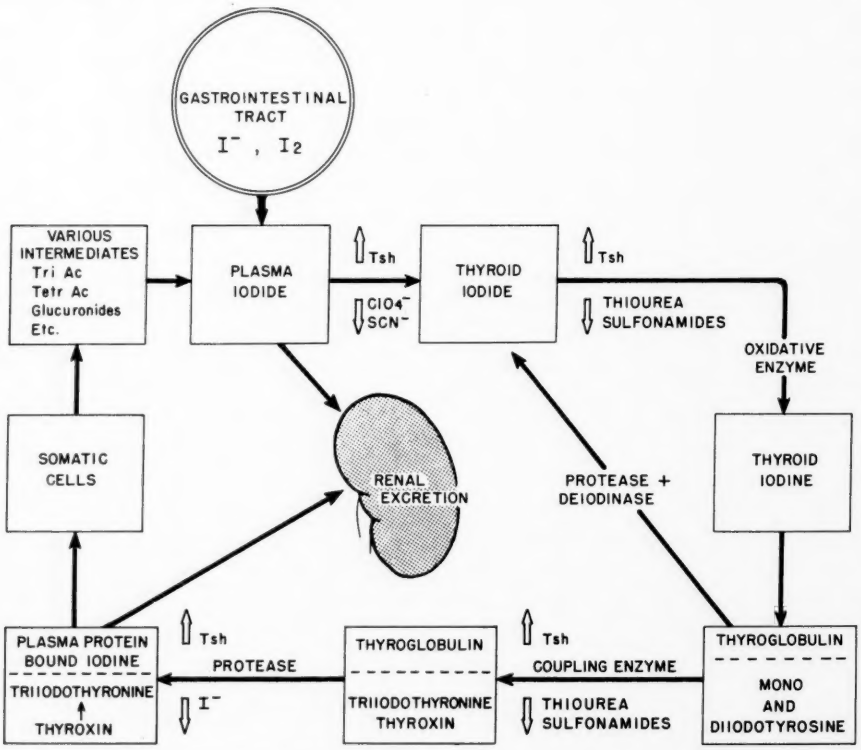

Fig. 1.—The metabolic circuit of iodine. *Open arrows* upward represent potentiation; *downward arrows*, inhibition.

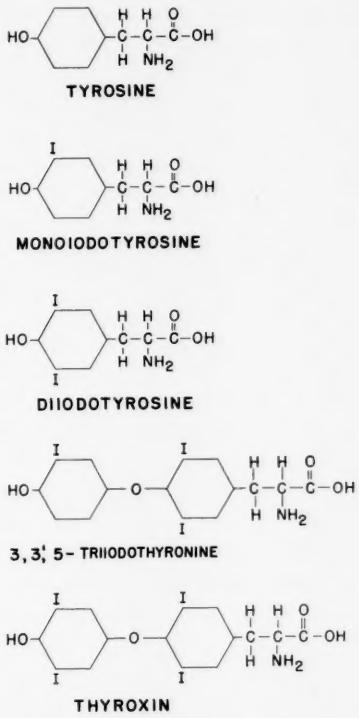

Fig. 2.—The principal and metabolically important iodinated amino acids.

IODIDE TRAPPING

The thyroid possesses a mechanism that permits concentration of iodide from the circulating plasma. Thyroids of various species contain approximately 80 per cent of the total body iodide, whereas the thyroid mass represents only 1/2,500 to 1/10,000 of the body weight.[3] The iodide cleared from the plasma by the thyroid is retained only momentarily in the gland as diffusible and dialysable inorganic iodide.[4] Only 1 to 2 per cent remains unbound to protein (the inorganic iodide space), but this amount is in much higher concentration than is the iodide in plasma. The normal resting thyroid contains a concentration gradient of iodide against the plasma of approximately 20:1. Iodide also becomes concentrated in salivary and gastric secretions. The gradient is similar to that in the thyroid. Secreting mammary tissue also has concentrating capacity. The iodine in these secretions appears to be in rapid equilibrium with the plasma, since, after the initial increase following the administration of I^{131}, the fall in labeled iodine in the saliva and gastric juice parallels the decrease in the plasma. The small inorganic iodide space of the thyroid is also readily exchangeable with the iodide of the plasma. It appears likely that the concentrating ability is not dependent on the further fate of iodine in the thyroid,[5] and it is clear that the capacity of the inorganic iodide space is limited.[6] Thus, with increasing plasma concentrations, a point is reached where the gland can take up no more iodide and the

thyroid-plasma ratio falls until it approaches the value for diffusion into the cell. The hypothesis that the concentrating stage is a rate-limiting step of hormone synthesis is supported by observations on a patient with goitrous hypothyroidism in whom a genetic defect in thyroidal iodide trapping was demonstrated.[7] The administration of potassium iodide obviated the need for a thyroidal pump and resulted in the disappearance of the symptoms and signs of hypothyroidism and marked diminution of the goiter.

The mechanism of the transport across the cell wall is largely unknown. It is probably enzymatically controlled, requiring an expenditure of energy. Trapping is oxygen dependent[8] and is inhibited by numerous substances that interfere with oxidative processes in cells as well as by sulfhydryl inhibitors.[9] Thiocyanate and perchlorate ions also prevent iodide trapping, the latter being about ten times as potent as the former.[10] It is not known whether these ions block trapping by interfering with cell membrane transport or by competing for binding sites within the gland, although it may be noted that thiocyanate has not been shown to be concentrated in the thyroid.

The role of the thyroid cell in hormone synthesis has not yet been ascertained. Early studies using autoradiographic techniques[11] suggested that very shortly after the administration of I^{131} it is concentrated and organically bound within the cell. Other workers[12] have observed the immediate appearance of I^{131} within the colloid. In these and in recent studies[13] it has been noted that even at the shortest time after the administration of I^{131} there is organically bound I^{131} within the cell. At this period it can be seen at the edge of the colloid very close to the cell apex, and with the passage of time to become distributed throughout the colloid. Similar studies[14] using tritium-labeled leucine have shown an initial uptake in the cell and only a gradual movement of the labeled protein to the apex of the cell and thence into the colloid. The speed at which this protein was distributed throughout the colloid was much slower than the distribution rate of organically bound I^{131}. These observations suggest that the cell is an iodine pump, and it is possible that iodine transport across it is intimately related to electrolyte transfer and carbonic anhydrase activity within the cell. In addition, the cell is responsible for synthesis of thyroglobulin and the specific enzymes required for hormone manufacture.

The thyroid-serum gradient is influenced by the state of the thyroid-pituitary axis. The ratio is enhanced by the administration of thyrotropin and depressed by hypophysectomy.[15] Suppression of thyrotropic secretion by administration of thyroxin also decreases the gradient. Hyperplastic glands customarily show a marked increase in iodide trapping.[16] This may be the result either of thyrotropin stimulation or iodide deficiency, or both. The latter may be more important, because an increase in the thyroid-plasma ratio appears in iodine-deficient glands before there is histologic evidence of thyrotropin stimulation.[15] This ratio provides a sensitive index of thyroid activity. If the hyperplasia is the result of the ingestion of antithyroid drugs, there will be depletion of thyroidal iodide and also impaired organification, resulting in an enlarged iodide space. The iodide in the space is discharged from the gland by administration of thiocyanate[16] or perchlorate. If either of these is administered after trapping has occurred, trapped

inorganic iodide is rapidly discharged from the gland, but iodine that has already been formed into iodinated tyrosines or thyronines is retained. The demonstration of the discharge of unbound iodide has been used to reveal the presence of impaired organification in certain pathologic states, as for example, one type of goitrous cretinism,[17] some cases of sporadic goiter often occurring in association with deaf-mutism,[18] and in Hashimoto's thyroiditis.[19]

OXIDATION AND ORGANIFICATION

After trapping, the iodide must be oxidized to an active form before it can displace the hydrogen from the 3- position of the tyrosyl residues. The oxidation and organification steps take place very rapidly, since very shortly after the administration of I^{131} nearly all the labeled iodine of the gland is bound to protein. It may be that oxidized iodide is immediately attached to tyrosyl residues or it is possible that there is an intermediate storage form of iodine which may in turn require the operation of a further enzymatic step in order to be transferred to tyrosine. Experimental evidence favors the latter concept, since a series of in vitro studies have suggested the presence of a "tyrosine-oxidase."[20,21] In many of these studies a compound has been shown chromatographically which, although not yet identified, may represent the "active" form of iodine.

The mechanism of the oxidation of iodide in the thyroid also remains uncertain. Accumulating evidence favors the importance of a peroxidase. Peroxidatic activity has been demonstrated many times in thyroid tissue, and, recently, specific iodide peroxidases have been described in thyroid and salivary gland homogenates.[22] Flavine cofactors also stimulate iodide utilization by thyroid preparations, but this may be due to the production of peroxide by the autooxidation of the reduced flavine. The requirement for copper noted by some workers may be merely due to its role as an oxidant, since it is not essential, nor can it restore iodination in boiled homogenates. It is of significance that the oxidation of iodide is inhibited by catalase[23] and the organification of iodide is inhibited by a variety of substances that affect the peroxidase system, including thiourea and resorcinol.

In the normal thyroid of most species, labeled mono- and diiodotyrosine are both almost simultaneously observed in the thyroid very rapidly after the administration of I^{131}. In the chick embryo, there is a considerable delay after the appearance of monoiodotyrosine before diiodotyrosine can be identified.[24] It is possible, therefore, that there is a separate iodinating enzyme for each and that the formation of monoiodotyrosine is (under normal conditions) rapidly followed by the second iodination to produce diiodotyrosine.

Chromatographic study of hydrolysates of the thyroid at varying times after the administration of I^{131} permits observation of the proportions of the iodoamino acids formed. Both mono- and diiodotyrosine rapidly appear. The relative amount of the latter steadily increases and, although the formation of thyroxin and some triiodothyronine is seen, the largest proportion of labeled iodine is found in the diiodotyrosine fraction. Studies in animals[25] and in patients with Graves' disease[26] have shown that the administration of drugs of the thiourea group results not

only in impaired organification, but also in inhibition of the conversion of mono- to diiodotyrosine, as demonstrated by an increase in the mono-diiodotyrosine ratio. This change can be produced by the administration of many other compounds and has been noted in many cases of nodular goiter. It is not clear, therefore, whether the phenomenon is indeed the result of a specific effect on an enzyme responsible for the second iodination or whether these agents have merely produced a relative iodide deficiency, a situation which does lead to the formation of more monoiodotyrosine than diiodotyrosine.[27]

"COUPLING REACTION"

Thyroxin is formed by the coupling of two molecules of diiodotyrosine and the extrusion of a side chain. Triiodothyronine is probably formed by the coupling of one molecule each of mono- and diiodotyrosine. This view is considered more likely than the possibility that thyroxin is partially deiodinated, especially since no thyroxin deiodinase has ever been demonstrated in the thyroid. Similarly, the failure to find thyronine in the gland makes it unlikely that thyroxin is formed by the iodination of this compound.

Coupling of diiodotyrosine to form thyroxin has been shown to take place in vitro. The reaction is slow, but the yield of thyroxin can be increased when small peptides containing diiodotyrosine are used.[28] Hence, it is likely that in the thyroid gland the coupling reaction does take place when diiodotyrosine is in peptide linkage within thyroglobulin. Little is known about the mechanism of this reaction. It is possible that a specific coupling enzyme is required, especially in view of the cases which have been described of patients in whom large goiters contained abundant iodinated tyrosines, but no iodinated thyronines.[2, 29] There may indeed be two specific enzymes for the formation of thyroxin and triiodothyronine, since analyses of some goiters have failed to demonstrate any thyroxin, although triiodothyronine was present.[30] The coupling enzyme may be closely related to the iodinating peroxidase, since a peroxidase can mediate the formation of a diphenyl ether linkage, similar to that in thyroxin, by oxidation of *p*-cresol.[31] Nevertheless, no enzyme which controls the coupling reaction has as yet been isolated.

It may be noted that some thyroxin formation can occur in thyroid slices incubated with I^{131} but little or none in cell-free homogenate systems. This may be due to the environment being unsatisfactory for an enzymatically controlled coupling reaction, but it may be the consequence of the lack of de novo synthesis of thyroglobulin by cell-free systems. Although the failure to obtain coupling could be the result of the diiodotyrosines not being in peptide linkage, the possibility also exists that coupling is merely a phenomenon dependent upon steric arrangements in thyroglobulin. The importance of favorable geometric relationship of the tyrosine molecules for their condensation has been emphasized by the demonstration that the formation of thyroxin does not occur during the iodination of silk fibroin despite the very high tyrosine content of this substance.[32]

THYROGLOBULIN

It is clear that thyroglobulin plays an important part in hormone synthesis

by providing a framework in which many of the reactions can take place. Indeed, it is likely that the key to unlocking many of the secrets of hormone synthesis lies in the unraveling of the mysteries of the nature of this compound. This large glycoprotein, with a molecular weight of approximately 650,000, was for many years considered to be the only iodoprotein in the thyroid. Recently at least two other iodinated constituents have been demonstrated in much smaller concentrations, but their biologic importance is not known.[33]

Thyroglobulin preparations were long considered to be homogeneous. However, ultracentrifugal studies have repeatedly shown several components with different sedimentation constants, and several bands are observed in starch gel electrophoresis. Similarly, heterogeneity is suggested by the demonstration of numerous discrete peaks in column chromatography studies,[34] and evidence has been provided that thyroglobulin possesses at least two antigenic components.[35] Nevertheless, it is possible that to a certain extent much of this apparent heterogeneity is physical in origin, since the proportion of the various components can be so readily altered by, for example, changes in pH. The concept exists that the molecule most commonly found is an aggregation of smaller components. It seems possible that aggregation does play an important part in producing the apparent heterogeneity of thyroglobulin, since elution of any one band from starch gel electrophoresis results in a 3- banded pattern when it is re-electrophoresed. Study of the various peaks by DEAE column chromatography shows that each possesses many similar characteristics, and it is possible that the differences could be due to variations in their relative iodination. These variations may in turn be related to the complexity of coiling of each molecule and thus explain why, even under the most favorable conditions of iodine supply, so relatively few of the tyrosyl residues in each molecule are iodinated.

Thyroglobulin possesses the additional function of providing an efficient means of storing large amounts of thyroid hormone. The thyroid gland of most species contains enough thyroid hormone for 2 to 10 weeks, provided there has been an adequate iodine supply. This is in marked contrast to nearly all the other endocrine glands, where only a 4- hour supply of hormone can usually be expected. Thus, it is possible for the thyroid to provide a constant daily secretion of hormone and vitiate any adverse effects of a variable dietary iodine.

HORMONE RELEASE

Before thyroid hormones can be released into the circulation, thyroglobulin must be broken down. Under normal circumstances no thyroglobulin or even small peptides have ever been demonstrated in the blood. In Hashimoto's thyroiditis, however, a frequent finding is the presence of an abnormal circulating iodoprotein. In patients with this condition a high titer of circulating antithyroglobulin antibodies can typically be demonstrated, and it is generally accepted that this disorder is characterized by autoimmunization by thyroglobulin.[36] It is not as yet clear whether a "leak" of thyroglobulin from the thyroid initiates the process or whether it is the result of some primary change in the thyroid itself. The initial damage may be produced by a separate distinct antibody, the

complement-fixing antibody, which has been shown to be located in the microsomal fraction of the cell,[37] and the activity of which is closely related to functioning activity of the thyroid.[38] The immunologic aspects of this disorder have become more and more complex. A colloid antigen other than thyroglobulin has been described and a cytotoxic effect of the serum of patients has also been shown.[39] Circulating antibodies are also found in other thyroid disorders, and it is of particular interest that elevated titers have been shown in apparently unaffected relatives of patients with Hashimoto's thyroiditis.[40]

Degradation of thyroglobulin is presumably performed in the thyroid by a series of lytic enzymes. Proteolytic activity has been demonstrated many times in the thyroid, being increased in toxic goiter and after thyrotropin administration, and decreased after hypophysectomy.[41] Proteases and peptidases have been isolated from the thyroid.[42] These have not been shown to be specific for thyroglobulin, and it has yet to be demonstrated that thyrotopin can produce a specific increase in the amounts of these enzymes.

As a result of proteolysis, thyroxin and triiodothyronine are released into the blood. Small quantities of free iodinated amino acids are found in the gland. Even though the quantity of free thyroxin is small, it is present in higher concentration than in plasma, thus establishing a gradient that will permit its passage from the thyroid. In addition, it may be noted that the binding of thyroxin to thyroglobulin is much lower than its binding to serum protein. The iodotyrosines which are also released from thyroglobulin are rapidly deiodinated in the thyroid by a potent deiodinase.[43] The iodine thus freed is conserved for reutilization. A deficiency of this deiodinating enzyme, producing impaired hormone synthesis as the consequence of the continuous loss of iodide from the gland, is the familial defect underlying some cases of goitrous hypothyroidism. Since these patients lack the enzyme throughout their bodies, the defect may be simply demonstrated by the administration of I^{131}-labeled iodotyrosines.[44] Examination of their urine will reveal the excretion of the iodotyrosine, unlike normal subjects in whose urine there will be only iodide.

Recently it has been suggested that an appreciable quantity of iodotyrosines is normally in the circulation.[45] The theoretical objections to such a concept of a pool of stable iodotyrosines have been countered by the suggestion that the iodotyrosines are very tightly bound to plasma proteins which protect them from the peripheral action of the deiodinase and also prevent exchange with administered labeled iodotyrosine. A very long biologic half-life is postulated to explain the failure of many workers to observe any significant labeling with I^{131}, even over prolonged periods. The methods that were employed to demonstrate the pool have been queried,[46] and no such pool has been found after attempts at repetitive labeling.[47] Nevertheless, although the concept is surprising on theoretical grounds, similar conclusions have been obtained elsewhere with the use of a completely different but very complex technique.[48] The existence of such a pool remains open to question, but seems improbable.

In attempts to estimate the rate of thyroid hormone secretion from the thyroid, a variety of methods have been employed.[49] The earlier involved studies of the amount of thyroid hormone or thyroxin required to maintain athyreotic

individuals in a euthyroid state, and subsequently of the amount of hormone required to suppress the thyroidal uptake and release of I^{131} of euthyroid individuals. Other techniques that have been employed include the measurement of the rate of incorporation or loss of radioiodine by the thyroid, with and without the administration of thyroid-blocking drugs, and calculations based on the kinetics of radioiodine between the thyroidal and extrathyroidal pools. The results of the various studies differ considerably, but it is now generally accepted that the normal daily secretion rate in man lies between 70 and 120 μg of thyroxin iodine.

HORMONE TRANSPORT

Most of the plasma thyroxin circulates in combination with protein. Several protein components do interact with thyroxin, but most of the hormone is attached to the "thyroxin-binding protein" (TBP).[50] On paper electrophoresis this has a mobility between α_1- and α_2-globulin, but a small fraction circulates in association with albumin and, possibly, another fraction moves with prealbumin. The distribution has varied in different reports according to the techniques employed, especially the nature and ionic strength of the buffer used.[51] In starch gel much of the thyroxin binding is found in the prealbumin zone. It has been suggested that this is the same protein that migrates with the globulins on paper,[52] but recent studies[53] favor there being several binding proteins.

It is now clear that only free thyroid hormones can leave the blood to enter the tissues. This has been demonstrated by studies in which the uptake of labeled hormone by erythrocytes was inhibited by serum as the result of TBP binding.[54] The equilibrium between the bound hormone and that free in the plasma is therefore of importance in governing the amount of hormone delivered to the tissues. The ability of TBP to bind thyroxin is limited. When increasing concentrations of labeled thyroxin are added to serum, the labeled iodine at first found in the inter-alpha zone is displaced to albumin and eventually is associated with almost all the other serum proteins in a nonspecific manner. The binding capacity varies in states of thyroid dysfunction and may therefore be employed as a diagnostic technique. Further, there is a marked specificity in the binding by TBP so that modification of the thyroxin molecule will result in alterations in the binding affinity.

In particular, triiodothyronine is much less firmly bound than thyroxin. This difference, reflecting the relative ease with which they may gain access to the tissues, may to a great extent explain the differences in metabolic response after the administration of these hormones.

The thyroid hormones are degraded in the peripheral tissues through several pathways. Iodide released by the degeneration of the hormones re-enters the iodide pool of extracellular fluids and thence becomes available for renal excretion or hormone synthesis.

SUMMARY

The thyroid gland performs its functions of synthesizing, storing, and

releasing the thyroid hormone by means of a complex sequence of linked chemical reactions. These include selective accumulation of iodine, iodination of peptide-linked amino acids, condensation of these into triiodothyronine and thyroxin, breakdown of thyroglobulin to its constituent amino acids, and secretion of the hormonal iodinated amino acids into the perfusing blood. The gland also must synthesize the thyroglobulin itself. There is reason to suppose that many types of thyroid disease occur because of inborn or acquired faults in specific steps in the metabolic processes of the gland. These errors may manifest themselves as hypothyroidism and goiter, but growth of the gland may permit a fully compensated rate of hormone production. It is not inconceivable that hyperthyroidism may also have a similar origin.

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THE METABOLISM OF THYROID HORMONES AS RELATED TO PROTEIN BINDING

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STRICTLY speaking, the function of an endocrine gland is fulfilled when it releases into the blood a quantity of hormone adequate to meet the needs of peripheral tissues. In the thyroid gland, this is accomplished through a series of well-ordered, internally and externally regulated reactions. However, this organization might prove fruitless if the hormone thus secreted were apportioned to the tissues in a purely random or haphazard manner. Fortunately, this is not the case, for beyond the thyroid there occurs a sequence of mechanisms for regulating the delivery of hormone to the tissues, where hormonal action and hormone destruction occur. These mechanisms have been the subject of increasing attention during the past ten years, not only because they provide a fertile area for pure physiologic exploration, but also because they may afford information concerning the manifestations and possibly the origin of certain thyroid diseases.

Following their secretion from the gland, thyroid hormones must traverse the circulation, enter the extracellular fluid, penetrate the cell, and affix themselves to those subcellular components where hormonal action or destruction takes place. A growing body of data indicates that the over-all disposal of hormone is modified by regulatory factors occurring at each of these stages.[1] The present discussion will be limited, however, to a consideration of the manner in which the disposal of hormone is regulated by the interactions which occur between the thyroid hormones and certain proteins of the extracellular fluid.

THE BINDING AND TURNOVER OF THYROXINE IN NORMAL MAN

There seems little doubt that, at least in terms of its concentration, thyroxine is the principal component of the circulating thyroid hormone.[2-5] For this reason, and because the vast majority of studies of hormonal metabolism have been concerned with thyroxine, this hormone has been chosen as the prototype for the present discussion.

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Although it was long recognized that the circulating thyroid hormone is somehow affixed to plasma protein, rendering it protein precipitable and neither dialyzable nor ultrafiltrable,[6,7] it was not until 1952 that evidence was obtained indicating that hormonal binding is effected by specific proteins. During electrophoresis of sera on filter paper in veronal buffer at pH 8.6, added I^{131}-labeled thyroxine was found to associate with a protein migrating in the zone between the α_1 and α_2 globulins.[8-11] This has been termed the thyroxine-binding protein (TBP) or thyroxine-binding globulin (TBG) of plasma. The identity of TBG as a specific entity is suggested by the fact that it can be isolated as an ultracentrifugally homogeneous protein whose avidity for thyroxine is exceedingly high.[12] Further electrophoretic studies in veronal buffer revealed that when the concentration of thyroxine in serum is increased by the addition of stable hormone, a progressively smaller percentage of the hormone is associated with TBG, while an increasing percentage migrates with albumin.[13,14] Calculation of the absolute amount of thyroxine bound to each protein discloses that the TBG in 100 ml. of normal human serum is capable of binding approximately 20 μg of thyroxine.[15] The binding capacity of albumin is, for practical purposes, unlimited.

In 1958, it was reported that, besides TBG and albumin, an additional protein in normal human serum is highly avid for thyroxine.[16] Binding of thyroxine by a protein migrating anodally to albumin was evident when serum was electrophoresed in filter paper in a buffer system containing trishydroxymethylaminomethane (TRIS) and maleic acid at pH 8.6.[16] Migration of thyroxine in a comparable zone was also noted during electrophoresis of serum in starch gel.[17] This protein, termed thyroxine-binding prealbumin (TBPA), has also been isolated from plasma and has been demonstrated to bind thyroxine strongly, although less so than TBG.[12] In normal human serum, the thyroxine-binding capacity of TBPA has been found to average approximately 120 μg per 100 ml.[18] Recently it has been suggested that TBPA binds thyroxine only in the presence of TRIS buffer.[19] However, hormonal binding by TBPA has been seen when serum is electrophoresed in a variety of other buffers, and the thyroxine-binding capacity in these buffers does not differ from that found in TRIS.[18,20,21] For this and other reasons,[18,21] it appears likely that TBPA is indeed a thyroxine-binding component of normal human plasma, although its importance relative to that of TBG in the circulation has not been clarified.

A variety of studies have indicated that the interaction of thyroxine with these several binding proteins conforms to a reversible binding equilibrium which can be formulated in the following manner[1]:

$$T_4 + TBG \rightleftarrows T_4 \cdot TBG$$
$$+ TBPA \rightleftarrows T_4 \cdot TBPA$$
$$+ Alb. \rightleftarrows T_4 \cdot Alb.$$

where $T_4 \cdot TBG$ represents thyroxine bound to TBG, for example, and T_4 represents unbound hormone.

The resultant of these interactions is expressed as follows:

$$T_4 + TBC_{EC} \rightleftarrows T_4 \cdot TBC_{EC}$$

where TBC_{EC} represents the sum of extracellular thyroxine-binding components.

From the foregoing formulation, it would follow that a portion, however small, of the thyroxine in plasma exists in the unbound or "free" state, and it has been suggested that it is this free moiety which is capable of penetrating or affixing to the cell.[15] Support for this hypothesis has been obtained in more complex in vitro systems containing extracellular thyroxine-binding protein, I^{131}-labeled hormone, and a cellular phase.[22] Under standard conditions of incubation the percentage of labeled hormone affixed to the cell is directly proportional to the concentration of hormone and to the mass of the cellular phase, and inversely proportional to the concentration of extracellular binding protein.[23] From results such as this, the following interaction has been proposed[1]:

$$\begin{aligned} T_4 + TBC_{EC} &\rightleftarrows TBC_{EC} \cdot T_4 \\ + TBC_C &\rightleftarrows TBC_C \cdot T_4 \end{aligned}$$

where TBC_C represents cellular thyroxine-binding components.

Here, the percentage uptake of hormone by the cellular phase would be directly dependent upon the proportion of hormone present in the free state. This relationship underlies recent diagnostic tests such as the "red cell uptake"[24] or "ion-exchange resin uptake,"[25] in which the percentile uptake of added labeled thyroid hormones from the patient's serum by a particulate system is ascertained. Results of such procedures in specific clinical states will be discussed below, but in general they are thought to reflect the state of the thyroid hormone-binding protein interaction in the patient's serum.

It is apparent that in physiologic systems the accumulation of hormone within the cell will also depend on the concentration and avidity of cellular binding sites. The existence of a "cellular TBG" has been suggested by recent electrophoretic studies of broken cell preparations.[26] To date, however, these have not been characterized, nor has it been possible to evaluate their hormone-binding activity with any degree of precision. Furthermore, except in the case of erythrocytes, sampling of cellular binding proteins in the human has not been feasible. In any event, it would appear from the foregoing formulation that, together with the cellular binding components, extracellular binding interactions regulate the proportion of extrathyroidal hormone localized within the cell. Since the degradation of hormone is an intracellular event, it would follow that hormonal binding interactions would regulate the proportion of hormone available to degradative systems. Provided that these systems metabolize a constant proportion of the hormone available to them, then the fraction of hormone degraded per unit time would ultimately depend upon extracellular binding interactions. For example, a lowering of the proportion of extracellular hormone present in the "free" state, such as would be occasioned by an increase in binding protein or a decrease in PBI, should be accompanied by a decrease in the over-all fractional rate of hormonal turnover.[1]

Concomitant assessment of extracellular binding and peripheral turnover of thyroxine in vivo have afforded a means of verifying this hypothesis. Following a single intravenous injection of I^{131}- labeled thyroxine, the administered hormone is distributed among the intravascular, interstitial,and intracellular fluids and ultimately mixes uniformly with endogenous unlabeled hormone in these sites.

This distribution equilibrium is achieved in 24 to 48 hours. Thereafter, disappearance of labeled hormone from the plasma reflects the fractional rate of disposal of hormone by peripheral tissues. This and other aspects of the peripheral metabolism of the hormone may be defined and calculated as follows[27]:

TDS = Thyroxine distribution space. The volume of body fluids which would be required to contain exchangeable thyroxine were it present throughout at the same concentration at which it exists in the plasma. This is calculated as the quotient of the quantity of labeled hormone which remains in the body and its concomitant concentration in the plasma.

ETT = The quantity of exchangeable thyroxine in terms of its content of iodine. This is believed to coincide closely with the quantity of extrathyroidal hormone.

k = Fractional rate of turnover of thyroxine. The fraction of hormone within the TDS which is degraded and replaced per unit time.

C = Thyroxine clearance rate. The volume of the TDS which contains a quantity of thyroxine equal to that being degraded per unit time.

HI = The concentration of hormonal iodine in the plasma. The PBI is most commonly employed as an approximation, and thyroxine is considered to be its major component.

D = Thyroxine disposal rate. The quantity of thyroxine undergoing disposal per unit time, in terms of its content of iodine. This is comprised of both hormonal excretion and metabolic degradation.

$$ETT = HI \times TDS$$
$$C = TDS \times k$$
$$D = HI \times TDS \times k$$
$$D = ETT \times k$$
$$D = HI \times C$$

In normal man, thyroxine is distributed through a virtual volume of 10 L. and turns over at a rate of approximately 10 per cent per day. Thus, a quantity of thyroxine equivalent to that contained in 1 L. of plasma is cleared from the thyroxine space each day. Calculated values for hormone disposal, based on the assumption that the average PBI of 5.0 μg per cent represents solely thyroxine iodine, therefore average approximately 50 μg of iodine daily.[27]

Comparable techniques can be employed to assess the peripheral turnover of other iodinated products.

PATHWAYS OF HORMONAL DISPOSAL

Under normal circumstances urinary excretion of thyroxine is negligible,[28,29] probably as the result of hormal binding in the plasma. Approximately 20 per cent of the peripheral disposal of thyroxine occurs by way of the feces, where the hormone appears mainly in the organic form.[27,30] The remainder of the peripheral disposal is effected by processes which liberate inorganic iodide from the hormone. On the basis of studies with thyroxine labeled in the 3′ and 5′ positions, two major catabolic pathways are present in tissues: direct deiodination of the diphenyl ether nucleus and oxidative deamination and decarboxylation of the

alanine side chain. The latter yields the pyruvic and acetic acid analogues of thyroxine, respectively, which then undergo deiodination. The majority of studies of hormonal degradation have been carried out in tissues obtained from small animals and the findings obtained have recently been reviewed.[31] Recent in vitro studies, however, have demonstrated the presence of such degradative enzymes in preparations of human leukocytes and kidney.[32,33] Their activity in preparations of human tissue appears to be much lower than that found in the rat, for example, in which the rate of turnover of thyroxine far exceeds that in man.

BINDING AND TURNOVER OF SEVERAL IODINATED PRODUCTS OTHER THAN THYROXINE

L-*3,5,3' Triiodothyronine* (T_3).—Electrophoretic studies indicate that T_3 is bound primarily to TBG and secondarily to albumin and other serum proteins. TBG binds T_3 less avidly than it does T_4, and T_3 can readily be displaced from TBG by small increments in the concentration of T_4.[34,35] In electrophoretic systems in which binding of thyroxine by TBPA is seen, T_3 is bound by TBG, but not by TBPA.[16] As a consequence of the less avid binding of T_3, the in vitro uptake of labeled T_3 by particulate systems, such as the erythrocyte or ion exchange resins, is considerably higher than the uptake of T_4. As might therefore be expected, the volume of distribution and fractional turnover of T_3 in man are both considerably greater than is the case with T_4.[36,37] This difference in the cellular penetration of the two hormones has been suggested as a possible explanation for the more rapid onset of action and the greater potency of T_3.

D-*Thyroxine* (D-T_4).—Electrophoretic studies in TRIS-maleate buffer reveal that, although bound little, if at all, by TBPA, D-T_4 is bound by TBG as avidly as is the naturally occurring isomer, L-T_4.[18] In vitro uptakes of D-T_4 have not been reported. D-T_4 is distributed more widely and turns over more rapidly than the natural form.[23,36] This difference in the metabolism of the two forms in vivo, however, may depend on factors other than extracellular binding, since tissue slices suspended in protein-free media display a higher uptake of D- than of L-T_4.[23]

Tetraiodothyroacetic Acid (TETRAC) and 3, 5, 3'-Triiodothyroacetic Acid (TRIAC).—With regard to protein binding, the acetic acid derivatives of T_4 and T_3 display profound differences from their parent compounds. Both TETRAC and TRIAC are bound primarily to TBPA, secondarily to albumin, and are not bound by TBG. Binding of TETRAC by TBPA is considerably more avid than that of TRIAC, and indeed the affinity of TBPA for TETRAC exceeds that for T_4.[18] Apparently, the intensity of the bond between TETRAC and TBPA is greater than that of the bonds between T_4 and either TBG or TBPA, since the in vitro red blood cell uptake of TETRAC is less than that of T_4.[38] Similarly, the uptake of TRIAC is lower than that of T_3.[38] In contrast to the relationship exhibited by the compounds previously discussed, in which hormonal binding and in vitro uptakes correlated well with relative rates of turnover in vivo, TETRAC and TRIAC are rapidly degraded.[39] Thus, the fractional rate of turnover of TETRAC is approximately twice that of T_4, while TRIAC is cleared so rapidly that, within a few hours after the intravenous administration of a tracer dose, it can no longer by identified in plasma.

This discordance between hormonal binding as assessed in vitro and hormonal turnover in vivo is disturbing, and illustrates the difficulties inherent in projecting in vitro data to the physiologic situation. However, several factors which are difficult to evaluate by current techniques may explain this apparent discrepancy. Thus, the avidity of red cell binding sites for these derivatives may not be representative of the avidity of binding sites in other tissues. Alternatively, local factors, such as pH, may modify the extracellular-intracellular exchange of hormone in vivo so that it differs from that seen in in vitro systems. Finally, TBPA may possibly serve as a vehicle for transporting hormone into the cell, thereby facilitating the turnover of compounds bound to this protein.

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THE TURNOVER OF THYROXINE IN STATES CHARACTERIZED PRIMARILY BY ALTERATIONS IN TBG

Ideally, the function of TBG would best be assessed by determining the effects of prolonged administration of this protein on hormonal metabolism in vivo, but sufficient quantities of purified protein have not been available. However, alterations in the binding activity of TBG have been found in several clinical states, and studies of hormone metabolism under these conditions have been generally consistent with the postulated function of this protein.[1,40] Under conditions in which the binding activity is increased, it would be anticipated that a smaller proportion of extracellular hormone would be present in the free state. As a consequence, the proportion of extrathyroidal hormone localized within the cell would diminish. In the face of an unchanged proportional rate of cellular degradation, the percentage of fractional turnover of hormone degraded would be less than normal. If hormonal supplies continued unabated, however, the concentration of hormone in the extracellular fluid would rise until the total amount of hormone disposed of was once again normal and equal to hormonal supply. Pronounced increases in the binding of thyroxine by TBG have been described in normal pregnancy[41,42] and in patients with hydatidiform mole.[43] However, extensive studies of the peripheral metabolism of thyroxine in these states have not been performed. Changes in the binding activity of TBG comparable to those which occur during pregnancy can be induced by the administration of pharmacologic doses of estrogen.[44] Here, the effects of hormonal metabolism conform closely to the postulated sequence described above.[45] Similar changes in the kinetics of hormonal metabolism and binding have been described in patients with acute hepatitis[46] and in a single eumetabolic subject with an apparently idiopathic increase in the binding activity of TBG.[20]

Conversely, where the binding activity of TBG is diminished, concentrations of PBI are low, hormonal turnover is accelerated, and total disposal of hormone is within normal limits. This situation obtains in patients given pharmacologic doses of androgens[47] and in a single patient with an idiopathic absence of TBG in the plasma.[48]

The complex metabolic abnormalities which occur in nephrosis complicate correlations between the binding of hormone in plasma and its peripheral turnover. In this syndrome, however, the binding activity of TBG is decreased,[15] PBI is low,[49] and extrarenal disposal of hormone is accelerated.[50]

As might be expected, the in vitro uptake of labeled thyroxine or T_3 from the plasma of patients with alterations in TBG varies inversely with the change in the binding activity of this protein.

THE TURNOVER OF THYROXINE IN STATES CHARACTERIZED BY ABNORMALITIES IN TBPA

The evidence for the physiologic function of TBG consists of a series of correlated changes in hormonal binding, as assessed electrophoretically, in the uptake of thyroid hormones by adsorptive systems in vitro and in the peripheral metabolism of the hormones in vivo. Similar, though less numerous, data are available on which to postulate a physiologic function for TBPA.

The in vitro red blood cell uptake of labeled thyroxine from serum, but not from simple buffer media at pH 7.4, is increased by the addition of trypan blue.[51] Recent electrophoretic studies in the authors' laboratory indicate that trypan blue in concentrations similar to those employed in uptake studies completely inhibits the binding of thyroxine by TBPA, without decreasing the binding activity of TBG.[12]

Similarly, the rate of dialysis of thyroxine from serum proteins at pH 7.4 is increased by the addition of salicylates[52] or veronal.[18]* Both agents decrease or completely inhibit the binding of thyroxine by TBPA without inhibiting the binding activity of TBG, as assessed electrophoretically.[18] Both salicylates[53] and barbiturates,[54] when administered in vivo, have been shown to accelerate the turnover of thyroxine. In the case of salicylates, this has been shown to be associated with the induction of hypermetabolism, which might be held responsible for the increase in hormonal turnover. However, in vitro studies of the enzymic deiodination of T_4 have failed to reveal an increase in hormonal deiodination in hypermetabolic tissue of animals given salicylates.[55] A decrease in the thyroxine-binding capacity of TBPA has been noted in a significant proportion of patients with various severe systemic illnesses, and a close inverse correlation has been found between the red blood cell uptake of T_4 and T_3 from the serum of such patients and the change in hormonal binding by TBPA.[56] In patients with comparably severe illness, the fractional turnover of thyroxine in vivo is increased.[55] Hypermetabolism was present in many of these patients, however, despite a lack of fever, and it is not possible to conclude with certainty that the abnormality in hormonal turnover was the result of changes in hormonal binding.

ABNORMALITIES IN HORMONAL BINDING AND TURNOVER IN PATIENTS WITH THYROID DISEASES

Abnormalities in hormonal binding and turnover have been described in

*The pH at which these studies were performed is emphasized since some question has been raised concerning the extent to which thyroxine is bound by TBPA at this pH. However, the observations cited, as well as the effects of trypan blue noted earlier, correlate well with electrophoretic evidence that these agents inhibit binding of thyroxine by TBPA. This would suggest that TBPA does indeed contribute to thyroxine binding in serum at physiologic pH. In studies with purified proteins at pH 8.6, the affinity of TBG for thyroxine is greater than that of TBPA and this difference is accentuated at pH 7.4. Nevertheless, at the lower pH, purified preparations of TBPA retain a pronounced thyroxine binding avidity, far greater than that of other proteins, such as albumin.[12]

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patients with myxedema and those with thyrotoxicosis. However, the complex metabolic changes associated with these disorders make it difficult to implicate alterations in hormonal binding as the cause of derangements in hormonal metabolism. Indeed, in the case of patients with Graves' disease, studies carried out after treatment strongly suggest that factors other than extracellular binding interactions play a primary role, as will be seen below.

In myxedema, the concentration of hormone in the plasma is low and the thyroxine-binding capacity of TBG is moderately increased.[15] These factors combine to decrease the proportion of hormone in the unbound or free state. As might therefore be expected, the uptake of labeled thyroid hormone from the serum of such patients is usually subnormal.[24] Occasionally, however, in vitro uptake values of labeled thyroid hormones from the serum of patients with myxedema are in the normal range. [57] These anomalous results may be correlated with the observation that in patients with severe myxedema, as in other severe illnesses, the binding capacity of TBPA may be decreased.[56] In vivo, fractional turnover of thyroxine is generally, but not invariably, decreased prior to treatment.[27,58] Hormonal concentration, binding, and turnover return to normal upon adequate therapy.[27]

In patients with thyrotoxicosis, the binding capacity of TBG is essentially normal, while the concentration of thyroxine in the plasma is increased.[15] This alone would lead to an increase in the proportion of hormone in the free state; in addition, in patients with severe thyrotoxicosis, the thyroxine-binding capacity of TBPA is often decreased.[56] Thus, percentile uptakes of thyroxine and T_3 by adsorptive particulate systems in vitro are abnormally high,[24] and in vivo the fractional turnover of thyroxine is almost invariably increased.[27,30,58]

ADDITIONAL FACTORS IN THE REGULATION OF THYROXINE TURNOVER

According to the sequence depicted earlier, describing the fate of thyroxine after its secretion from the gland, several factors other than extracellular thyroxine-binding equilibria may be conceived of as potential regulators of hormonal disposal. Principal among these are the cellular binding sites for hormone and the intracellular mechanisms for hormonal degradation or excretion. Several lines of evidence indicate that such factors do indeed contribute to the alterations in over-all hormonal disposal which occur in certain abnormal states.

The role of cellular metabolic rate in regulating hormonal degradation has come under consideration. In man, the induction of thyrotoxicosis medicamentosa with either thyroxine or T_3 is associated with an increase in the fractional rate of turnover of thyroxine.[59] Changes in the thyroxine-binding proteins under these conditions have not been demonstrated, and, in patients treated with T_3, the concentration of thyroxine in the plasma declines. Thus, factors within the cell, rather than extracellular binding interactions, would appear to be responsible for the altered hormonal turnover in this condition. This view is supported by the finding that induction of myxedema or thyrotoxicosis in animals results in a decrease or increase, respectively, in the rate of thyroxine deiodination when tissues of such animals are studied in systems free of extracellular binding protein.[55,60] Nevertheless, such changes in the rate of hormonal degradation cannot

necessarily be ascribed directly to changes in metabolic rate, since they may represent a response of degradative enzymes to altered availability of substrate or to other factors as yet unconsidered.

Several pharmacologic agents which induce hypermetabolism also accelerate hormonal turnover. The uncertainties concerning the mechanism whereby salicylates alter hormonal turnover have been discussed earlier, and similar considerations apply to dinitrophenol. The latter agent also decreases binding of thyroxine in serum as assessed by dialysis techniques,[52] increases the rate of disappearance of thyroxine from the plasma of rats[61] and probably of man,[62] but fails to increase the rate of deiodination of the hormone when studied in isolated hypermetabolic tissue in vitro.[55] Adrenaline is also a calorigenic agent which, in the rat, has been shown to speed the turnover of thyroxine.[63] However, its possible effects on hormonal binding, as well as upon the intracellular mechanisms for hormonal degradation, have not been evaluated.

Thus, conclusions concerning the role of cellular oxidative metabolism in regulating hormonal turnover must be held in abeyance. Nevertheless, there remains evidence that other intracellular factors are responsible for modification of hormonal degradation under certain circumstances. Acceleration of the peripheral turnover of thyroxine has been noted in patients with Graves' disease following restoration of a normal metabolic state,[59] in certain of their close relatives who have never been thyrotoxic,[64] and in some young girls with nontoxic "adolescent" goiter.[12] In all these situations, it has not been possible to demonstrate abnormalities in extracellular hormonal binding interactions.

Finally, the recent demonstration that, in vitro, serotonin and other indoles produce both qualitative and quantitative changes in pathways of thyroxine metabolism[65] raises the possibility that these and other naturally occurring compounds may influence the peripheral turnover of thyroid hormone under physiologic circumstances.

It is apparent that while much has been learned in the field of hormonal transport and metabolism within a relatively short time, much still remains to be discovered. Nevertheless, the hoped for elucidation of physiologic and pathogenetic mechanisms, which largely stimulated interest in this field, has already been partially realized.

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CERTAIN ASPECTS OF RENAL FUNCTION IN MYXEDEMA

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THE diuretic effect of potent thyroid extract in myxedema was described and emphasized before the turn of the century.[17] Since then a relation between thyroid hormone activity and renal function has been demonstrated in a variety of experimental circumstances.[8,49,52] However, precise definition of this relationship is not entirely clear at the present time.

It may be well to review briefly some of the effects on the kidney of diminished or absent thyroid function in experimental animals.

EXPERIMENTAL HYPOTHYROIDISM

Many of the apparent contradictions in the literature are probably attributable to differences in the following experimental considerations: the particular species studied, the time elapsed between ablation of the thyroid gland and the experimental period, the dose and duration of hormone administration, the state of function of other endocrine glands, and other details of experimental design (for example, anesthesia) which influence renal function. Only a small proportion of the available literature will be considered.

Thyroid ablation in growing animals has a definite retarding influence upon the rate of growth and development of the animal as a whole, including the kidney.[57] Renal tissue may be especially vulnerable to thyroid deprivation as evidenced by the fact that partial thyroidectomy under certain conditions may have an adverse effect on renal development without retarding whole body growth.[57] On the other hand, thyroidectomy in the mature rat does not preclude normal capacity for compensatory hypertrophy of the remaining kidney after unilateral nephrectomy has been performed.[36] Although the mechanism of the effect of thyroid ablation on renal development is not known it is possible that it is related to the observed disturbances in the metabolism of renal tissue.[20,44,57]

In addition to these effects there are certain well-defined changes in renal function associated with decreased thyroid activity. Thus reduction in glomerular filtration rate (GFR) and maximum tubular capacity for Diodrast excretion (T_{mD}) have been observed in dogs and noted to revert toward normal with thyroid replacement therapy.[8,60] It is also interesting that the thyroidectomized

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dog has little if any change in GFR and Tm_D after the administration of pituitary anterior lobe extract. This is similar to the observation in the adrenalectomized dog and quite different from the normal or hypophysectomized animals which respond to the administration of anterior lobe extract with large increments in GFR, renal plasma flow (RPF), and Tm_D.[60]

The role of thyroid hormone in the renal excretion of water has captured the interest and attention of many investigators but continues to be poorly defined. The administration of thyroid hormone to normal animals produces little if any diuresis, but may result in an enhanced capacity for a diuretic response to administered water.[31,49] That this effect is related to some alteration in the kidney itself is suggested by the observation that the kidney of a thyroid-treated dog transplanted into a normal animal responds to saline infusion with greater diuresis than a simultaneously transplanted kidney from a normal control animal.[11] These authors believe that more studies are required before this observation may be interpreted with certainty. Of great interest are the observations that thyroidectomy results in marked reduction in the polyuria of experimental diabetes insipidus in several species.[18,19,43] The administration of thyroid extract under these conditions is followed by a recurrence of the polyuria. That this effect of thyroidectomy is not a function of hypometabolism per se is indicated by the observation that the administration of dinitroorthocresol results in increased metabolism without change in the polyuria associated with diabetes insipidus.[59] The precise mechanism of this effect is not known, although the reduction in GFR after thyroidectomy may play a role. It has been suggested that the administration of thyroid hormone in large doses may decrease the renal responsiveness to antidiuretic hormone (ADH) activity in the dog.[27] Further studies are required for substantiation of this concept. Whatever the mechanism, it is interesting that thyroidectomy has been employed with some success as a therapeutic measure in patients with diabetes insipidus.[7] Despite the reduction in urine volume following thyroidectomy in animals with diabetes insipidus, there is evidence that thyroid ablation does not increase the susceptibility to water intoxication.[24]

Although many details are omitted in this review, and much remains unknown, it is clear that thyroid ablation in the experimental animal results in the following general effects on the kidney: altered cellular metabolism; retarded rate of growth and development; decreased GFR, RPF, and Tm_D; and modified excretion of water under certain conditions.

With this brief background in mind we shall turn our attention to observations in the human being with decreased thyroid function.

CLINICAL MYXEDEMA

Despite the presence of renal dysfunction in patients with myxedema there is usually no evidence of clinically significant impairment of renal function.[8] While some patients may have proteinuria the remainder of the urinalysis is usually quite normal and azotemia is not a feature of the disease.[46]

Renal Hemodynamics (*Table I*).—The clearance of urea, perhaps largely a reflection of glomerular filtration rate, has been observed to be reduced in

TABLE I. RENAL HEMODYNAMICS IN PATIENTS WITH MYXEDEMA

INVESTIGATORS	YEAR	GFR (ML./MIN.)*		RPF OR RBF (ML./MIN.)		TM (MG./MIN.)†		FF (%)	
		A‡	B‡	A	B	A	B	A	B
Corcoran and Page[13]	1947	55.0 33.6	101 80	509§ 448§	600§ 617§	11.1 13.6	37.3 32.7	17 11	27 18
Davies et al.[15]	1952	72 55 81 62 48 90		435§ 560§ 633§ 354§ 467§ 520§					
Hlad and Bricker[29]	1954	82.6 82.4 78.0 76.3 61.6	98.1 115.8	476‖ 318‖ 459‖ 383‖ 343‖	355‖ 464‖	 55.0 54.7		17.3 25.9 17.0 19.9 18.0	27.7 25.0
Yount and Little[63]	1955	58 93 75 40 42 86 49		340‖ 330‖ 315‖ 153‖ 299‖ 250‖ 244‖				18.6 28.0 24.8 26.0 14.2 34.6 20.6	
Bleifer et al.[6]	1960	99 87 138 92 107 96 95 118	117 108 194 112 119						

*Clearance of inulin, except for Bleifer et al. who determined endogenous creatinine clearance.
†Tm_D in Corcoran and Page; Tm_{PAH} in Hlad and Bricker.
‡A, Before treatment with thyroid; B, After treatment with thyroid.
§Renal blood flow (RBF) (Corcoran and Page—Diodrast; Davies et al.—PAH).
‖Renal plasma flow (RPF) (clearance of para-aminohippurate).

patients with myxedema, and to revert toward normal after suitable replacement therapy has been instituted.[4,35,64] Inulin clearance, a more precise index of GFR, as well as renal plasma flow, has been found to be decreased in patients with myxedema.[13,15,29,63] Similarly, treatment with potent thyroid principle results in return of these functions toward normal. Although endogenous creatinine clearance may have been within the broad range of normal in the study of Bleifer and co-workers,[6] treatment with thyroid substance was followed by an increase in clearance in each instance studied. The exact time required for improvement is not clear in most studies, since the data provided generally refer to restudy after the patient was considered to be "euthyroid," "stable," or the basal metabolism rate had returned to normal. However, the observations of Hlad and Bricker[29] are most interesting. One patient with total thyroidectomy

was given 100 μg of l-triiodothyronine intravenously and clearances of inulin and para-aminohippurate (PAH) were determined for 90 minutes after injection. No changes in renal hemodynamics were noted in that time. The patient was then given 100 μg of l-triiodothyronine intravenously every day for 6 days and restudied. In that interval, inulin clearance had risen from a pretreatment value of approximately 82 ml. per minute to a posttreatment value of 115 ml. per minute, whereas the PAH clearance had increased from 318 ml. to 464 ml. per minute.

The precise mechanism for the reduction in renal hemodynamics in patients with myxedema is not known. It may well be that the observed decrease in cardiac output associated with myxedema is responsible.[15,47] In addition, a possible role of chronic anemia cannot be excluded.[9]

Filtration fraction (FF), that is, the proportion of the renal plasma flow that is filtered (GFR/RPF), is quite variable in this disease.[13,29,63] This is not completely understood, but partial explanation may be found in the possibility that the clearance of PAH (even if extraction ratio is determined by renal vein catheterization) may, under certain conditions, underestimate actual renal blood flow rather than provide a precise measure of it.[48,54] The authors are reluctant to utilize these measurements for the determination of sites of altered renal resistance.

Tubular Function.—To the best of our knowledge, renal concentrating ability has not received a great deal of detailed inquiry in patients with myxedema. Beaumont and Robertson[4] performed the Fishberg dehydration test on 7 patients with untreated myxedema. The mean specific gravity was 1.025. One patient had a specific gravity of 1.021, whereas in the other 6 the specific gravity ranged from 1.024 to 1.027. Although these observations suggest that at least some significant degree of concentrating ability is preserved in myxedema, the available data cannot preclude some subtle diminution in the capacity to elaborate a concentrated urine. Several months after treatment had been instituted the same patients were restudied and the mean specific gravity after dehydration was 1.018, no patient having a urine with specific gravity greater than 1.023. Dietary conditions and values for solute excretion are not provided in the report. Although treatment seems to have resulted in lowered specific gravity of the urine, we do not believe that the effects of treatment upon renal concentrating ability can be stated with confidence at this time. Since the patients were restudied at a time when they were not likely to be undergoing diuresis, the latter may not serve to explain any difference noted in this one study. In 2 cases of myxedema reported by Zondek and Wolfsohn[64] there was normal concentrating power although detailed observations were not provided.

Phenolsulfonphthalein (PSP) excretion has been studied in patients with myxedema with results that are somewhat difficult to interpret. Lerman and Brogan[32] gave PSP intramuscularly to patients with hypothyroidism and to others with hyperthyroidism and measured the amount of PSP excreted in 130 minutes. They found that there was less PSP excretion in patients with myxedema than in those with hyperthyroidism. The authors concluded, however, that PSP excretion was probably within normal limits in both groups of patients.

Zondek and Wolfsohn[64] observed definite reduction in the excretion of indigo carmine in 2 patients with myxedema. The maximal tubular excretion of Diodrast or PAH is reduced in clinical myxedema and reversible with treatment.[13,29] These observations suggest that patients with myxedema may have some impairment of renal tubular function. The extent and precise nature of this dysfunction are not known, although several investigators have indicated that these abnormalities may be related to alterations in renal tissue metabolism. Corcoran and Page[13] have pointed out, however, that one cannot exclude the importance of other hormonal factors (for example, anterior pituitary) that are affected by decreased thyroid function and may influence renal tubular secretory activity. In addition, the possibility of intrarenal circulatory disturbances involving the tubular cells may be mentioned.

Water Excretion.—There are several reports indicating that patients with myxedema have impaired capacity for water diuresis while other observations indicate a normal diuretic response to water loading. These discrepant reports are difficult to interpret in view of differences in experimental design. In some instances the quantity of water administered may have been insufficient to inhibit antidiuretic hormone maximally, thus making comparison with other subjects, including normal individuals, exceedingly difficult if not impossible. The interval between urine collections also differed from one study to the next, perhaps obscuring differences in maximum diuretic response to administered water. Since there is a wide range in the normal response to water loading, a response considered "normal" might well be reduced for an individual patient. Indeed, in some studies in which a response is considered "normal," there are no data which compare pre- and posttreatment responses. Since there is a normal diurnal rhythm of sodium and water excretion, differences in the time of water loading may also account for discrepant observations.

In 1946, Levy and his associates[33] reported a "negative" water test in 3 patients with myxedema. This meant simply that the volume of any hourly specimen of urine voided in the morning (after a single water load of 20 ml. of water per kilogram of body weight, as defined in the Robinson, Power, Kepler test[45]) exceeded the total volume of urine voided between 10:30 P.M. of the preceding night and 7:30 A.M. on the morning of the water load. Obviously one cannot be certain that the response to water administration under these conditions was entirely "normal" or maximal for any individual, despite the fact that normal individuals similarly have a "negative" test by the same criteria.

The studies of Garrod and his associates are extremely interesting and demonstrate some of the problems involved in interpreting "normal" and "abnormal" responses. In 1952, Garrod and Burston[22] referred to unpublished observations of Garrod which indicated that patients with hypothyroidism had "no undue delay or failure of water diuresis." In 1954, Garrod and Gilliland,[23] employing a single water load of 20 ml. per kilogram of body weight, reported that 16 of 18 patients with primary myxedema had urine flow in excess of 3 ml. per minute during the second hour after ingestion of the water load, and more than 50 per cent of the volume of the administered load was excreted in a 3 hour period. These values were decidedly above those observed in patients with hypopituitarism

(less than 1.5 ml. per minute in the second hour after loading and less than 20 per cent of the volume of the administered load was excreted in 3 hours). However, it is not clear that the patients with myxedema had a perfectly normal diuretic response to water. First, precise comparison with the normal cannot be made from the data presented and, second, pre- and posttreatment data in individual patients were not provided. One of the 2 patients with extremely poor response showed improvement after thyroxin administration while the other patient with poor response did not improve after cortisone. That this group of investigators has noted a definite impairment in water diuresis in patients with myxedema is suggested in a letter by Fraser and Garrod[21] addressed to the editor of *Lancet* in 1954. This communication indicates that moderately severe failure of water diuresis may occur in patients with primary myxedema. Furthermore, these authors stated that the diuretic response may revert to normal after thyroid replacement treatment and that the abnormality is not corrected by cortisone.

In 1954, Crispell and his co-workers, employing the Robinson, Power, Kepler water test, noted distinct abnormality in water diuresis in 10 of 11 patients with primary myxedema compared with normal control subjects.[14] This abnormality was defined largely as a markedly reduced fraction (42 per cent, compared with the normal of 90 per cent) of the administered load excreted in the 4-hour period after the administration of water. In addition, in 8 of the 10 patients the night urine volume exceeded any single hourly volume of urine after loading. The only patient without demonstrable abnormality in water diuresis had had myxedema for only 3 months after radioiodine treatment. It was also shown that decreased intestinal absorption of water was not a major factor in the production of abnormal diuretic response, since the diuresis following the intravenous infusion of glucose solution was also impaired. These investigators studied the possible role of adrenal insufficiency in the impaired diuretic response to water. Six patients with abnormal diuretic response were given cortisone orally in doses sufficient to improve impaired water diuresis of patients with Addison's disease. While one patient had a "normal" response to water after cortisone was administered there was no significant effect of steroid administration on the diuretic response in the other 5 patients. Two patients given thyroid treatment alone had normal response to ingested water after they became euthyroid. Interestingly, 2 patients, receiving thyroid but still apparently hypothyroid, responded in normal fashion after the administration of cortisone. One of these patients had previously failed to respond to the steroid when no thyroid was given. The authors concluded that the diuretic response to administered water was impaired in patients with myxedema and that this impairment responded to the administration of thyroid substance but failed to respond to the administration of cortisone.

In 1955, Hubble[30] employed the Robinson, Power, Kepler water test in the study of 4 patients with myxedema. He found that 3 patients excreted 1 ml., 4.5 ml., and 3.5 ml. per minute in the second hour after water loading with a 3 hour excretion of 26, 48, and 60 per cent of the volume of the administered load, respectively. For his normal values the authors quoted direct communication from Garrod who gave a lower limit of normal of 5 ml. per minute urine flow in

the second hour after water loading and 70 per cent of the volume of the total administered load excreted in 3 hours. The fourth patient had a response that was within the normal range, 10.5 ml. per minute in the second hour and 90 per cent of the load excreted in 3 hours. In 2 of the 3 patients with abnormal response by these criteria, improvement was noted after thyroid replacement treatment. In the third patient there was no significant change after 21 days of therapy.

In 1955, Oleesky[40] reported the results of water loading studies in 9 patients with primary myxedema. After overnight dehydration, a water load of 1 L. was given orally and the urine collected at intervals of 15 to 20 minutes for 2½ hours. The maximal rate of urine flow in these 9 patients with myxedema varied from 2.5 to 11.0 ml. per minute, with a mean value of 6.3 ml. per minute. These results are quite different from those observed by the same investigator in a study of patients with hypopituitarism.[39] In the latter group the maximal urine flow under similar circumstances varied from 0.9 to 2.5 ml. per minute. However, from the data presented, it cannot be determined that the response of the patients with hypothyroidism was completely normal. No posttreatment data are available.

In 1958, Moses and co-authors[37] reported the results of water loading in 9 patients with primary hypothyroidism. The water load consisted of 1,500 ml. of water given by mouth over a period of 15 to 45 minutes to patients who had fasted the preceding night. The urine volume from the beginning of the test to 5 hours thereafter was collected and measured. The authors considered a urine volume of less than 800 ml. in this 5-hour period to be abnormal. The 9 patients with hypothyroidism excreted more than 1,000 ml. of urine in this 5-hour test period and therefore were considered to have a "normal" response. Although the total amount of urine excreted in this 5-hour period may fall within the range of normal, it is difficult to be certain that the peak or maximal response to water loading was entirely normal. The frequency of collections was not such that this parameter of water diuresis could be determined.

In 1960, Bleifer and co-workers[6] studied 8 patients with untreated primary myxedema. In each instance a water load in the form of isotonic hexose solution was administered intravenously within a 1 hour period to provide a load of 20 ml. per kilogram of body weight. Seven of the 8 patients were also studied with an oral water load. Urine specimens were collected at approximately half-hour intervals until maximal rates of urine flow were achieved. In the laboratory in which these tests were performed it had been observed that the maximal rate of urine flow under these conditions varied widely in normal individuals over a range extending approximately from 8 to 25 ml. per minute. In the 8 patients with myxedema the maximal urine flow varied between 4.4 and 26.9 ml. per minute with only 2 patients having flows of less than 8.0 ml. per minute under these conditions. Consequently, by these criteria, 6 of the 8 patients might have been considered to have a "normal" response to administered water. Five patients were restudied after thyroid therapy had been observed to exert a favorable clinical response. In each instance, including patients with values within the "normal range" before treatment, there was an increment in the maximal rate of urine flow of from 1.4 to 6.1 ml. per minute. In each case the increase in

diuretic response to administered water following replacement therapy was associated with an increase in endogenous creatinine clearance. In 4 of the 5 patients studied, the urine during the period of peak flow after treatment was more dilute than it had been prior to therapy and in 1 patient the urine was more concentrated in the posttreatment study. In 3 patients the increased diuretic response to administered water following treatment with thyroid substance was associated with an increase in the rate of solute excretion, whereas in one subject the rates of solute and sodium excretion were lower in the posttreatment than in the pretreatment test. In one instance there was virtually no difference in solute excretion between pre- and posttreatment studies.

A discussion of the mechanism for any impairment in water diuresis warrants consideration of three major determinants of water excretion: the level of antidiuretic hormone activity, the rate of solute excretion (in particular, sodium), and the rate of glomerular filtration. In the studies of Bleifer and his associates, the role of ADH activity is not entirely clear since 4 of the 5 patients elaborated a urine more dilute after treatment than before therapy. One cannot exclude that an increase in ADH activity imposed some limitation on the pretreatment diuretic response to water in these patients. However, it is extremely difficult to conclude with certainty the role of antidiuretic hormone activity in any situation which is also associated with concomitant changes in the rate of solute excretion and endogenous creatinine clearance. The role of solute excretion in producing the change in water diuresis after therapy is also not entirely clear since 2 patients with a posttreatment increase in water diuresis had no augmentation in solute excretion. The only consistent finding that correlated with the increase in water diuresis after thyroid replacement therapy in these patients was a significant increase in endogenous creatinine clearance.

In summary, it is apparent that patients with primary myxedema may well have a reduction in the diuretic response to administered water. It is also clear from a variety of observations referred to above, including those of Bleifer and co-workers, that the diuretic response to administered water in myxedema is rarely as seriously impaired as it is in patients with hypopituitarism. Consequently, the water test may serve a useful purpose in differentiating primary from secondary hypothyroidism. The mechanisms of the impaired response to administered water in patients with primary myxedema are not entirely established. The role of antidiuretic hormone and solute excretion remains unclear. However, the impaired water diuresis that is observed may be attributed to a reduction in glomerular filtration rate which is noted in this disease.

Sodium Excretion.—As the term myxedema (mucinous edema) implies, the swelling associated with adult hypothyroidism bears certain resemblances to, but also shows certain apparent differences from, the edema associated with congestive heart failure, Laennec's cirrhosis, and the nephrotic syndrome. These differences are apparent clinically, histologically, and chemically.[8,10] In the more common varieties of edema it is well established that: (1) total body sodium content is increased, (2) there is expansion of total extracellular fluid volume, and (3) this increase in body sodium is due to enhanced renal retention of sodium

by mechanisms that are presently not entirely established.[5,58] The data relevant to the precise role of the kidney in the formation of myxedema are even less clear.

Certain evidence indicates that at some time in the course of myxedema an accumulation of excess sodium in the body occurs.[1,12,38] Since the kidney is the major organ responsible for sodium elimination, an accumulation of excess sodium in the body, of necessity (with the exception of local dislocations of fluid), implies that the kidney is excreting less sodium than the organism is receiving. This phenomenon may be related to intrarenal disturbances or to extrarenal factors influencing a normal kidney to retain sodium. In the case of myxedema, an additional possibility exists; namely, a moiety of the ingested sodium may not be available for renal excretion. In myxedema there is an increase in the mucopolysaccharide content of many tissues.[61] It has also been suggested that various cations, including sodium, may exist in association with certain mucopolysaccharides and behave as if they were incompletely ionized.[16] If this applies to myxedema and is an important mechanism for sodium accumulation, it could not account for water retention since the sodium would then be osmotically inactive. It has been suggested that mucopolysaccharides may have certain hydrophilic properties resulting in water accumulation.[10]

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The evidence that patients with myxedema may accumulate sodium in the body follows. With the institution of appropriate thyroid replacement therapy there is often a diuresis of sodium-containing fluid, suggesting the delivery of extracellular fluid.[12] Although normal values of exchangeable sodium have been reported in myxedema,[2] other studies indicate an increase in this measurement which is further observed to decline with therapy.[1,38] In addition, the volume of distribution of radiosodium is reportedly increased.[1] On the other hand, patients with myxedema have been given 10 Gm. of sodium chloride daily for 3 days without any observed weight gain, whereas patients with rheumatic heart disease similarly studied demonstrated decided gain in weight.[15] This type of observation, however, does not exclude the possibility that the patient with myxedema had a positive balance of sodium earlier in his course and had reached a new equilibrium state and no longer had a tendency toward sodium accumulation at the time of study. Such a thesis may be likened to that postulated to explain observations in the patient with cirrhosis and ascites in a stable state.[42] These patients who are neither gaining nor losing weight can excrete an administered salt load extremely well. Additional study of salt excretion in myxedema is needed to clarify this point.

Assuming the existence of sodium accumulation, the possible role of "binding" of sodium with mucopolysaccharide has already been considered. We should now consider the role of the kidney. It must be emphasized that there is little positive evidence that allows conclusions concerning the role of the kidney in the handling of sodium in patients with myxedema. As just mentioned, this disease is frequently if not usually associated with a decrease in glomerular filtration rate. Since the concentration of sodium in the serum is generally normal or only slightly reduced in myxedema, the lowered GFR may result in a decreased filtered load of sodium which in the absence of altered tubular function may be associated with decreased sodium excretion.[1] In other states associated with

edema, there is considerable evidence that there is increased tubular reabsorption of sodium.[58] Whether or not such a phenomenon occurs in myxedema is not established. If there is increased tubular reabsorption of sodium in myxedema, there is the possibility that it is related in some fashion to the altered tubular cell metabolism known to occur in this disease. On the other hand, it may be that increased tubular reabsorption of sodium occurs and that it is due to extrarenal factors influencing tubular handling of sodium in an indirect fashion. For example, in the case of Laennec's cirrhosis, an argument has been presented for the possibility that there is a decrease in the "effective" extracellular fluid volume, despite an increase in total volume.[41] Such a decrease in volume may act as a stimulus for sodium reabsorption.[53,58] Perhaps a similar mechanism is operative in myxedema. Indeed a decrease in blood volume has been described.[25] If "volume" is a factor in this condition the means by which it is appreciated and then transmitted to the kidney are not known. It has been suggested that the "volume factor" in normal individuals and in patients with edema may be mediated via the adrenal cortex and the secretion of increased quantities of aldosterone.[3] Measurements of adrenal function in myxedema are somewhat contradictory,[62] but certain observations suggest a decrease in adrenal cortical activity.[34,50,51] Furthermore, urinary aldosterone excretion has been reported to be within the normal range in this condition.[28,34] Perhaps these observations indicate that the mechanisms of sodium accumulation in myxedema may differ from those in other edematous states in which an increase in aldosterone excretion has been observed, although the role of aldosterone is not entirely clear even in heart failure, cirrhosis, or the nephrotic syndrome.[41,55]

Pericardial effusion[26] and ascites[56] are known to occur in myxedema without apparent explanation. In addition, the role of heart disease and heart failure in sodium accumulation has not been defined in patients with myxedema.

SUMMARY

The patient with myxedema may have several abnormalities in renal function. Glomerular filtration rate and renal plasma flow may be reduced. Maximum tubular capacity for the excretion of Diodrast or para-aminohippurate may be reduced. The ability to excrete administered water is limited in patients with myxedema although not to the same extent as it is in patients with hypopituitarism. The difference in the ability to excrete water in these two conditions may be employed as a test to differentiate one from the other. Although the mechanisms for impaired diuretic response to administered water in patients with primary myxedema are not entirely known, the defect may be attributed to a reduction in glomerular filtration rate. While there is evidence that the patient with primary myxedema accumulates excess sodium in the body, relatively little is known about the mechanism whereby this is accomplished. In particular, relatively little is known about the role of the kidney in this regard.

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ALTERATIONS OF PROTEIN METABOLISM IN MYXEDEMA

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"WITH the exception of the reduction in total energy exchange, perhaps the most conspicuous alteration in the athyrotic state is that in protein metabolism."[1] This statement by Means clearly poses the problem which is the subject of this presentation. Protein abnormalities in myxedematous patients have interested investigators for some time, and it is the purpose of this communication to summarize some of these studies. An attempt will be made to correlate studies from our laboratory with those in the literature in an effort to formulate a working concept of abnormalities of protein metabolism in patients with myxedema. Experimental investigations in animals which apply to this problem will also be reviewed.

STUDIES IN MYXEDEMA WITH THE USE OF TAGGED AMINO ACIDS

We have previously reported studies of amino acid metabolism in adult patients with myxedema using the tagged amino acid, N^{15} glycine, and employing the method of San Pietro and Rittenberg.[2,3] In brief, this method is based upon the assumption that dietary amino acids interact with tissue constituents at a rapid rate and that a dietary amino acid is either used for protein synthesis or is catabolized and excreted as urea nitrogen.

Fig. 1, modified from San Pietro and Rittenberg,[2] illustrates this principle. The metabolic pool (P) is defined as the mixture of nitrogenous compounds derived from the diet and from the breakdown of body nitrogen. Dietary nitrogen enters this pool where part is used for protein synthesis. Another part is catabolized to urea, mixes with the urea pool, and is excreted in the urine. The total urea in the body constitutes the urea pool. For the steady state, dietary nitrogen equals nitrogen excretion, and the rate of protein breakdown equals the rate of protein synthesis.

The small amount of N^{15}-labeled glycine which is introduced into the metabolic pool at time zero will be used for protein synthesis or catabolized to urea and excreted. The relative distribution of the N^{15} between the protein and urea pools will be a function of the rate of urea excretion and the rate of protein synthesis. If one excretory pathway, that of urea, can be completely defined, then it is

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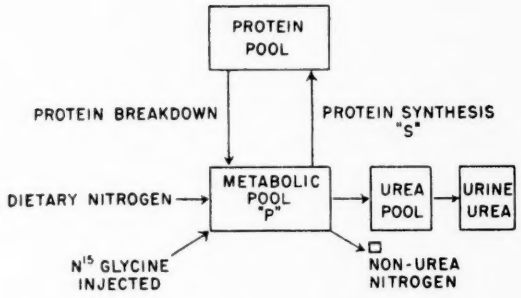

Fig. 1.—A schematic diagram of the N^{15} glycine method. (From Crispell, Parson, and Hollifield: J. Clin. Invest. 35:164, 1956; modified from San Pietro and Rittenberg.)

possible to calculate the rate of protein synthesis and the size of the metabolic pool. This calculation is based upon the assumption that the total transfer of nitrogen from any pool is proportional to the size of that pool. Since the rates of protein synthesis are different in various organs, it is apparent that this protein synthesis rate is a measure of the total rates of synthesis for the whole organism.

As reported previously[4] the protein synthesis rate in 5 healthy volunteers averaged 776 mg. of nitrogen per kilogram per 24 hours, and in 6 patients with myxedema it was reduced to an average of 354 mg. of nitrogen per kilogram per 24 hours (Fig. 2). This occurred despite the fact that patients with myxedema were in moderately positive nitrogen balance as established by classical nitrogen-balance studies. The administration of l-triiodothyronine to a patient with myxedema over an 8 month period resulted in a synthesis rate above the normal level (Fig. 3). The patient at this time was euthyroid and in nitrogen equilibrium, as established by classical nitrogen-balance studies. These studies indicate that the absence of thyroid hormone results in an over-all decrease in the rate of protein synthesis. This decrease is corrected by the administration of thyroid hormone.

Epelbaum and Dergousova[5] have studied protein metabolism in rats made hypothyroid by the oral administration of 6-methyl-thiouracil for a 30 day period. The technique used was the subcutaneous administration of the amino acid, methionine, labeled with radioactive sulfur, S^{35}. The amount of radioactivity incorporated into various tissue proteins 24 hours after the injection of the radioactive material was determined in the hypothyroid rats and in a group of control subjects. The protein of the liver, kidney, and spleen of the hyopthyroid rats incorporated 20 per cent less of the radioactive-labeled amino acid as compared with the control group. This study suggests that the anabolism of tissue proteins is decreased in the hypothyroid rat.

DuToit,[6] using an in vitro slice technique, has studied the effect of thyroid hormone on the incorporation of the amino acid alanine, tagged with C^{14}, into the proteins of the rat liver.

The amount of tagged alanine incorporated in liver proteins by liver slices from thyroidectomized rats was markedly reduced when compared with that of

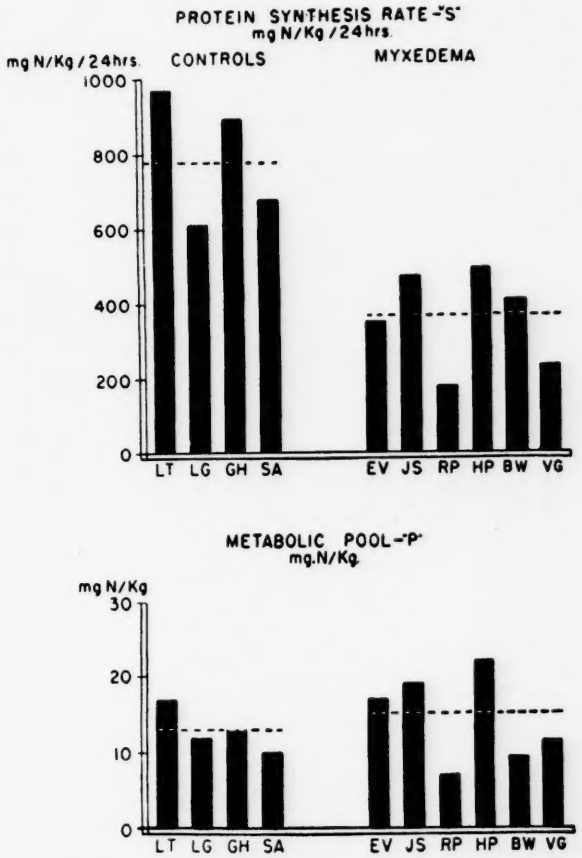

Fig. 2.—A comparison of the rate of protein synthesis and the size of the metabolic pool in healthy volunteers and patients with myxedema. The broken horizontal lines represent the average for the various groups. (From Crispell, Parson, and Hollifield: J. Clin. Invest. 35:164, 1956.)

normal control animals. The liver slices from the athyrotic animal given thyroxine incorporated a normal amount of tagged alanine in liver proteins. These in vitro studies correlate quite well with studies described above for the intact animal and suggest that the incorporation of amino acids into protein is decreased in the absence of the thyroid hormone.

The problem of decreased catabolism with the amino acid technique has been studied in rats by Hoberman and Graf,[7] using glycine labeled with isotopic nitrogen, N^{15}. If the amount of the N^{15} given and the amount excreted in the urine over a given period are known, it is possible to analyze the data mathematically and calculate the rate of breakdown of body proteins to amino acids. Their studies suggest that in the recently thyroidectomized rat there is a decrease in the catabolism of body proteins to amino acids. The administration of thyroxin to thyroidectomized rats restored the rate of catabolism to control levels.

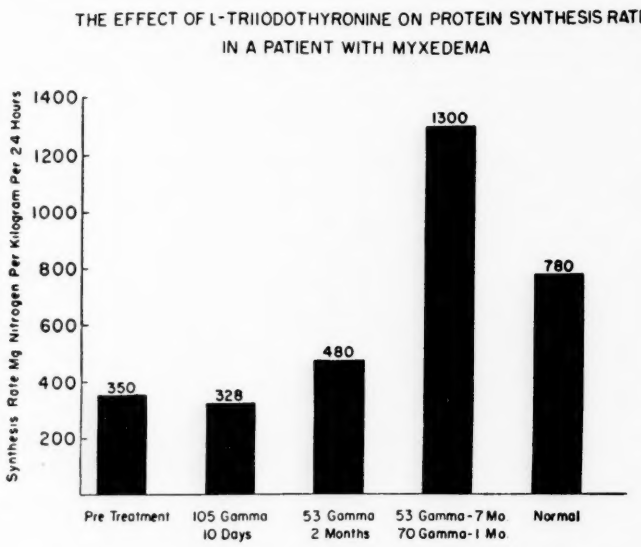

Fig. 3.—A comparison of the protein synthesis rate of a patient before and after therapy with l-triiodothyronine with the rates of healthy volunteers. (From Crispell, Parson, and Hollifield: J. Clin. Invest. 35:164, 1956.)

STUDIES IN MYXEDEMA WITH THE USE OF TAGGED SERUM PROTEINS

Schwartz[8] has studied the degradation rate of human serum albumin, labeled with radioactive iodine, in 2 adults with myxedema. The rate of degradation was decreased before treatment and was returned to a normal level after 10 weeks of thyroid therapy. This study suggests that there is decreased catabolism of serum proteins in the untreated patient with myxedema. Lewallen, Rall, and Berman[9] also used I^{131} iodoalbumin to study this problem. Their data were subjected to a very rigorous mathematical analysis, and, "The analysis indicated that there is an increase in total exchangeable albumin in myxedema which is confined to the extravascular compartments, a reduction in the rate of albumin synthesis and catabolism, a reduction in the fractional rate of albumin catabolism, an increase in the transcapillary transport rate of albumin, and a reduction in plasma volume." Iber and his co-workers[10] also showed by the I^{131}-labeled serum albumin technique that the administration of l-triiodothyronine to euthyroid patients would increase the rate of catabolism of the labeled albumin.

CLASSICAL NITROGEN-BALANCE STUDIES IN MYXEDEMA

Classical nitrogen-balance studies in cases of long-standing myxedema in the untreated adult have demonstrated that these patients are usually in positive nitrogen balance.[4,11,12] The administration of thyroid hormone to these patients produces a significant negative nitrogen balance which persists for several weeks. A metabolic study of one such patient under treatment with 100 μg of l-triiodothyronine daily produced negative nitrogen balance lasting for about 200 days before attaining nitrogen equilibrium.[13] The administration of the same amount of l-triiodothyronine to euthyroid subjects produces minimal negative

nitrogen balance and is of much shorter duration than in the patient with myxedema.[14]

The athyrotic child with a potential for growth has a different pattern of response to the administration of thyroid hormone than do the adult patients with myxedema. In an excellent study of a 4½-year-old cretin, reported by Wilkins,[15] the period of negative nitrogen balance while receiving thyroid hormone lasted only 15 days and was then followed by a long period of positive nitrogen balance with an associated spurt in growth. Johnston and Maroney[16] have also demonstrated that the administration of thyroid hormone to children with hypothyroidism will produce positive nitrogen balance and growth.

Numerous studies have demonstrated that the administration of thyroid hormone will restore the rate of growth in an athyrotic animal with a growth potential. This is associated with nitrogen retention as demonstrated by the studies of Rupp and his associates[17] who gave physiologic doses of thyroxin to thyroidectomized rats and produced a decrease in urinary nitrogen excretion. Pickering and Fisher[18,19] demonstrated the same effect in young athyrotic monkeys and their studies were especially significant in that the decrease in urinary nitrogen occurred with increased protein intake.

NEGATIVE NITROGEN BALANCE IN ADULT PATIENT WITH MYXEDEMA GIVEN THYROID HORMONE

The source of the increased urinary nitrogen after the administration of thyroid hormone to an adult patient with myxedema has intrigued investigators for many years. The pattern of excretion of nitrogen, water, and electrolytes has also been used to postulate the type of protein metabolic defect occurring in these patients.[20,21,22] Boothby and colleagues[20] proposed that the patient with myxedema had an increase in "deposit protein." This term "deposit protein" was introduced by Lusk[23] to designate protein dissolved in body fluids surrounding the cells in contrast to the "tissue or organized" protein. It was supposedly the first substance given up by the body during starvation. This concept was introduced in the era before the concept of the dynamic state of protein metabolism was established and, therefore, does not seem applicable at the present time.[3,24] However, Boothby's conclusion that "in the myxedematous patient there is an excess of albuminous fluid as compared with a normal individual" may be valid.

Histochemical examination of biopsy and autopsy material[25,26,27] from patients with myxedema has demonstrated a definite increase in mucoproteins and also that these substances disappear from the skin after treatment with thyroid hormone. Mucoproteins are thought to consist of protein components tightly bound to highly polymerized polysaccharides, examples of which are chondroitin sulfate and hyaluronic acid.[28] Hyaluronic acid is composed of glucuronic acid and N-acetylglucosamine and contains approximately 3.2 per cent nitrogen. Wiener and co-workers[29] were able to show a moderate increase in the urinary excretions of hexosamines in a myxedematous patient receiving thyroid therapy. The metabolism of these mucoproteins after the administration of thyroid may contribute to the negative nitrogen balance, but Albright[22] has pointed out that they

cannot be the chief source of the increased urinary nitrogen, the reason being that the negative nitrogen balance is accompanied by an increased excretion of phosphorous and potassium "two elements which are contained in traces in mucoproteins." Byrom[21] studied the excretion of electrolytes and nitrogen by myxedematous patients receiving thyroid. In his study, during the initial fall in weight, nitrogen was excreted with small amounts of potassium, but subsequently potassium and nitrogen were excreted in proportions more characteristic of cellular destruction. The results during the initial period could possibly be explained by the "mobilization" of mucoproteins and the subsequent results by a resumption of normal catabolic processes.

We have carried out studies in an attempt to gain insight into the mechanisms of the negative nitrogen balance following institution of therapy with thyroid hormone. A 29-year-old woman with classical myxedema of approximately 5 years' duration was placed on the metabolic unit where a short time balance study was performed by the usual technique. After a 15 day control period she was given 50 mg. of dinitrophenol daily for 10 days and then 100 μg of l-triiodothyronine daily for an equal period of time. The dinitrophenol raised the basal metabolism rate (BMR) from -32 to -7 without any change in urinary nitrogen excretion, but the l-triiodothyronine raised the BMR from -32 to only -17 per cent and produced the expected increase in urinary nitrogen. It was shown many years ago by Dodds and Robertson[30] that dinitrophenol would not change the clinical status of the myxedematous patient even though the BMR was raised to normal levels. This study, as just described, suggests that the elevation of the BMR per se does not cause the increased urinary nitrogen and that the thyroid hormone either causes, or is at least "permissive" in, this catabolic process.

SUMMARY AND WORKING HYPOTHESIS

The studies which have been reviewed and presented appear to be compatible with the concept that in the myxedematous patient receiving thyroid hormone a small portion of the increased urinary nitrogen comes from the catabolism or mobilization of mucoproteins which have accumulated during the hypothyroid state. The bulk of the urinary nitrogen appears to come from normal tissue or at least from tissue with a normal potassium to nitrogen ratio. In the adult, who is no longer growing, this could be due to the resumption of the normal catabolic rate which was decreased during the hypothyroid state. It would appear that, in the untreated patient, the decreased protein synthesis rate, as measured by the isotopic technique, and the positive nitrogen balance are compatible with a decreased turnover of protein. The administration of thyroid hormone causes an increase in the turnover of protein as manifested by an increase in synthesis rate and negative nitrogen balance. In the athyrotic child, with a growth potential, the administration of thyroid causes increased turnover of protein with a resumption of the normal growth pattern. As growth is associated with nitrogen retention this would account for the short period of increased nitrogen excretion followed by the long period of nitrogen retention.

Olsen[31] in reviewing the role of hormones in protein metabolism has stated

that the action of the thyroid hormone on amino acid metabolism has not been elucidated. In our opinion the studies reported are compatible with the possibility that thyroid hormones act by increasing the transfer of amino acids across cellular membrane similarly to the action of insulin on glucose metabolism.[32] This possibility, now open to experimental trial, is under investigation with the use of the amino acid technique described by Noall and his group.[33]

CONCLUSIONS

1. The use of an isotopic technique has demonstrated that the rate of protein synthesis is markedly decreased in adult patients with long-standing myxedema. The administration of thyroid hormone returned the rate to that of healthy volunteers. The assumptions which are made in order to provide a mathematical interpretation of the data may or may not be correct. The observed fact is that the rate at which dietary nitrogen exchanges with body nitrogen is decreased.

2. Classical balance studies in adult myxedematous patients given thyroid hormone demonstrate a long period of negative nitrogen balance with an eventual return to nitrogen equilibrium. In the athyrotic child, on the other hand, the administration of thyroid hormone produces a short period of negative nitrogen balance followed by a long period of nitrogen retention and growth.

3. The absence of thyroid hormone in the human being appears to be associated with a decrease in the turnover of protein with both anabolism and catabolism decreased.

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ABNORMALITIES OF CHOLESTEROL METABOLISM IN HYPOTHYROIDISM AND THE EFFECTS OF TREATMENT WITH THYROID HORMONES AND THYROXIN ANALOGUES

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THE nature of the remarkable influence thyroid hormones have on the metabolism of cholesterol has been the subject of much study. Progress has been stimulated by the isolation and crystallization of the active principle of the thyroid gland by Kendall[1] in 1915, the synthesis of thyroxin by Harington and Barger[2] in 1927, the establishment of 3,5,3′-triiodo-L-thyronine as a natural thyroid hormone in 1952 by Gross and Pitt-Rivers[3] and by Roche, Lissitzky, and Michel,[4] and intense and growing interest in cholesterol and the development of isotope techniques for investigating biochemical processes.

This paper will survey: (1) current thoughts on the abnormalities of the metabolism of cholesterol in hypothyroidism, (2) clinical correlations between serum lipids, the basal metabolic rate, and disorders of the thyroid gland, (3) the effects on serum lipids of treating hypothyroidism with the thyroid hormones and some of the newer thyroxin analogues, and (4) the "dissociation" of thyroid hormonal effects on serum cholesterol and basal metabolic rate in human beings with myxedema. Where necessary for the argument, information about euthyroid and hyperthyroid states will be included.

ABNORMALITIES OF CHOLESTEROL METABOLISM IN HYPOTHYROIDISM

The pathway of cholesterol biosynthesis has been formulated in considerable detail since the demonstration by Bloch and Rittenberg[5] in 1942 that all the carbon atoms of cholesterol can be provided by acetate alone. Of the many steps on the way from acetate to cholesterol, the intermediate formation of mevalonic acid and later of squalene seems to be obligatory. Thyroid hormones appear to exert their influence on cholesterol synthesis at a step between acetate and mevalonate (Fig. 1).[6]

The direction of effect of thyroid hormones is clearly toward greater synthesis of cholesterol. It was shown in 1949 by Karp and Stetten[7] that the rate of incorporation of deuterium from body water into cholesterol is decreased in rats with hypothyroidism and increased in rats with hyperthyroidism. Pretreatment of rats with thyroxin stimulates, and thyroidectomy depresses, the incorporation of deuterium into cholesterol in the liver, intestine, kidney, and spleen.[8] Both

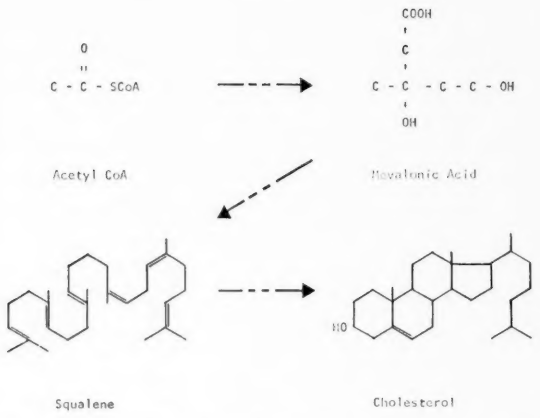


Fig. 1.—Four essential stages in the pathway of cholesterol biosynthesis. Thyroid hormones exert their influence between acetate and mevalonate.

I^{131} ablation of the thyroid and thiouracil administration decrease liver synthesis of cholesterol. (Thiouracil, administered to thyroidectomized rats, also has an extrathyroidal effect in the same direction.[9]) The synthesis of cholesterol in connective tissue[10] and in the lung[8] was reported to be unaffected by changes in thyroid status.

Since thyroid hormones increase biosynthesis of cholesterol but decrease concentrations of serum cholesterol, an accounting of what happens to the cholesterol balance is needed. It has been shown that excess cholesterol disappears rapidly from the serum of hyperthyroid rats and slowly from the serum of rats with hypothyroidism.[11] The degradation of administered radioactive cholesterol and the excretion of cholesterol and of some of its acidic products is increased by desiccated thyroid.[12] There is no clear-cut evidence of a difference in total body cholesterol between small animals with hypothyroidism and hyperthyroidism.[11,13,14] Thyroactive compounds given to hypothyroid (or euthyroid) animals presumably increase the breakdown and excretion of cholesterol more than they increase the synthesis of cholesterol. In myxedema, the decreased degradation and elimination of cholesterol presumably are sufficient, despite decreased synthesis, to account for the characteristic hypercholesterolemia.

The workshop for cholesterol metabolism is the liver, where a major portion of synthesis takes place. Cholesterol is altered in the liver and excreted in the bile. Cholesterol concentration in the bile decreases after rats are made hypothyroid,[11,15,16] and increases when they are made hyperthyroid.[11,16] The secretion of cholic acid in the bile is reduced in hypothyroid rats.[15,16] It is also reduced by pro'onged giving of T_3,[15] Triac,*[15] or desiccated thyroid.[16] Although the biliary cholic acid excretion is decreased in the hyperthyroid rat, the total excretion of bile acid is normal because of an accompanying increase in excretion of chenodeoxycholic acid.[17] In the rat with hypothyroidism, formation of both cholic

*Abbreviations of thyroid hormones and analogues are defined in Table I.

TABLE I. IDENTIFYING NAMES AND ABBREVIATIONS OF THYROID HORMONES AND ANALOGUES REVIEWED IN THIS PAPER*

COMPOUNDS	ABBREVIATIONS IN THIS PAPER	OTHER ABBREVIATIONS IN THE LITERATURE
Desiccated thyroid		
3,5,3′,5′-Tetraiodo-L-thyronine	L-T_4 L-Thyroxin	Tx
3,5,3′-Triiodo-L-thyronine	L-T_3	L-Triiodothyronine, Trit, Liothyronine, Trith, TRIT, TRITh
3,5-Diiodo-L-thyronine	L-T_2	DITh
3,5,3′,5′-Tetraiodo-D-thyronine	D-T_4 D-Thyroxin	Dextro-thyroxin
3,5,3′-Triiodo-D-thyronine	D-T_3	D-Triiodothyronine
3,5-Diiodo-D-thyronine	D-T_2	
3,5,3′,5′,-Tetraiodothyroformic acid	Tetraform	T_4F, $TForm_4$, T_4-FA, TETRFOR
3,5,3′-Triiodothyroformic acid	Triform	T_3F, T_3FA
3,5,3′,5′-Tetraiodothyroacetic acid	Tetrac	T_4A, TA_4
3,5,3′-Triiodothyroacetic acid	Triac	T_3A,TA_3, TRITA, TRIAC, TRIAc
3,5,-Diiodothyroacetic acid	Diac	T_2A, TA_2
3,5,3′,5′-Tetraiodothyropropionic acid	Tetraprop	T_4-Prop, T_4-PA Tetprop
3,5,3′-Triiodothyropropionic acid	Triprop	T_3-Prop, T_3-PA
3,3′,5′-Triiodo-DL-thyronine	3,3′,5′-T_3	T'_3, Reverse-T_3, Iso-T_3, Reverse TRIT, 3,3′,5′-Trit

*The abbreviations in the second column are based in part on suggestions in the literature.[149]

and chenodeoxycholic acids is diminished.[17] In man, single doses of 0.2 to 0.4 mg. of L-T_3 have been reported to cause a transient fall in the ratio of biliary chenodeoxycholic to cholic acid excretion.[18]

The chenodeoxycholic acid excreted in increased amount in the rats with hyperthyroidism is conjugated with taurine.[17] In man the normal ratio of glycine-conjugated to taurine-conjugated bile acids is about 3 or 4 to 1, but in myxedema it may be 8 or 10 to 1.[19] The administration of thyroid to hypothyroid patients has been reported to bring ratios of elevated glycocholate to taurocholate within normal limits.[20]

The complex interrelations of the metabolism of cholesterol and bile acid are greatly influenced by any interference with the enterohepatic circulation. The concentration of bile acids in the blood coming to the liver influences the hepatic rate of cholesterol degradation, or bile acid synthesis, so that a feed-back control mechanism exists.[21] The concentration of plasma cholate is increased in hypothyroid and decreased in hyperthyroid rats, and the administration of cholate causes an increase in serum cholesterol.[11] Beyond all this the intestinal flora affect the enterohepatic circulation and may alter thyroid hormones administered orally.[22]

Direct studies of cholesterol metabolism in man are of interest. Gould and his co-workers[23,24] showed that the treatment of myxedematous patients with desiccated thyroid, L-T_4 or D-T_4, caused a prompt increase in the incorporation of acetate-C^{14} into plasma free cholesterol. The total cholesterol concentration fell as treatment continued. An estimate was made of the free and total cholesterol content of the liver-blood pool of a euthyroid and a myxedematous man (Table II).

TABLE II. ESTIMATE OF FREE AND TOTAL CHOLESTEROL OF THE LIVER-BLOOD POOL IN A EUTHYROID AND A MYXEDEMATOUS 70 KILOGRAM MAN[24]

	EUTHYROID PATIENT				MYXEDEMATOUS PATIENT			
	CHOLESTEROL CONCENTRATION (MG./100 ML.)		CHOLESTEROL CONTENT (GM.)		CHOLESTEROL CONCENTRATION (MG./100 ML.)		CHOLESTEROL CONTENT (GM.)	
	FREE	TOTAL	FREE	TOTAL	FREE	TOTAL	FREE	TOTAL
Plasma	61	202	1.7	5.6	142	474	3.1	10.4
Erythrocytes	150	150	3.4	3.4	150	150	2.7	2.7
Liver	255	300	4.6	5.4	293	420	5.3	7.6

Lipsky and his associates[25] gave acetate-1-C^{14} to patients with severe myxedema and concluded that hepatic synthesis of cholesterol was decreased and that there was a decrease in peripheral utilization of the sterol, both of which became normal after treatment with T_3. Other data are consistent with a low rate of cholesterol synthesis in man.[26,27]

Kurland and others[28] present a detailed report of studies of 2 patients who were given C^{14}-labeled cholesterol before and after the induction of myxedema with radioactive iodine. No change in the rapid increase of red blood cell free cholesterol was seen in myxedema. The half life of plasma free cholesterol was estimated to be 75 and 69 days before radioactive iodine treatment and 164 and 118 days, respectively, after the patients became hypothyroid. Formation of labeled esterified cholesterol was delayed in myxedema. The calculated "exchangeable cholesterol pool" was 60 and 79 Gm. in the 2 patients; it was unchanged in myxedema. A third patient died 15 days after the injection of labeled cholesterol. Postmortem examination showed that the specific activity of the liver was higher than that of any other tissue and was in equilibrium with plasma. The data were considered consistent with a more marked decrease of cholesterol disposition than of cholesterol synthesis in myxedema.

The relationship between thyroid hormones, certain steroids, and cholesterol has been studied in man by Hellman, Gallagher, and their co-workers.[29-31] They reported a very low production of androsterone and a reduced conversion of testosterone-4-C^{14} in myxedema, with reversion to normal after administration of T_3. Androsterone administered directly to myxedematous patients and to both hypercholesterolemic and normocholesterolemic euthyroid patients caused a re-

duction in serum cholesterol. This leads to the speculation, unsubstantiated so far, that androsterone might mediate the thyroid hormonal effect on serum cholesterol, at least to some degree.

There are a number of recent reviews of the broad field of cholesterol metabolism,[32-34] of the relationships between hormones and cholesterol metabolism,[35-37] and of the role of thyroid hormones in the biosynthesis, catabolism, and excretion of cholesterol.[24,38-40]

CLINICAL CORRELATION BETWEEN SERUM LIPIDS, THE BASAL METABOLIC RATE, AND THYROID DISORDERS

In his earliest reports of the physiologic activity of his "Group A" or "alpha-iodin" compound, from which thyroxin crystals were obtained, Kendall[41-45] described classical thyroid hormone effects on growth, mental activity, skin, hemoglobin, oxygen consumption, heart rate, and the electrocardiogram, but he made no mention of cholesterol.

Denis[46] in 1917 reported the concentrations of blood cholesterol in a wide variety of conditions, including a few cases of thyroid disease. Although he attached no diagnostic significance to these measurements of cholesterol, the data are interesting: in 5 cases of severe hyperthyroidism the mean cholesterol content was 186 mg. per 100 c.c. of blood (range 163-231); in 5 cases of mild hyperthyroidism, it was 231 (range 186 to 257); and in 1 case of myxedema, it was 295.

About the same time Luden[47] reported that doses of Kendall's thyroxin given to a myxedematous patient caused a fall in cholesterol and a rise in basal metabolic rate (BMR) and that 4 single doses on consecutive days produced progressive reciprocal changes in the blood cholesterol concentration and the BMR. In 1922 Epstein and Lande[48] presented data showing elevated BMR and low blood cholesterol levels in cases of exophthalmic goiter, normal BMR and cholesterol in patients with nontoxic goiter, and a tendency to low basal metabolic rates and high blood cholesterol levels in patients with hypothyroidism. Gardner and Gainsborough[49] reported in 1928 a poor correlation between plasma cholesterol and BMR in patients with exophthalmic goiter, but they were impressed by the hypercholesterolemia found in untreated patients with myxedema. Their most fully investigated case of hypothyroidism showed a definite fall in cholesterol concentration and rise of BMR on treatment with thyroxin or thyroid.

Mason and co-workers[50] in 1930 reviewed the literature on the relationships between cholesterol and thyroid, and pointed out that some authors had doubted the validity and significance of the apparent inverse relationship between the BMR and cholesterol concentration. They also presented data on 47 patients with hyperthyroidism and 23 with hypothyroidism, and showed that in individual cases the blood cholesterol level may have correlated poorly with the BMR, but that, in general, it was low in hyperthyroidism and high in hypothyroidism. They emphasized as a most striking feature of myxedema the fall in blood cholesterol to normal as the BMR returns to normal during treatment.

The nature of the relationship between serum cholesterol level and the basal metabolic rate was of continuing interest. Grabfield and Campbell[51] failed

to establish a relationship between the two in 100 consecutive patients without thyroid disease. In a series of papers on blood cholesterol in thyroid disease, Hurxthal[52-54] noted that hypercholesterolemia accompanied spontaneous myxedema and myxedema caused by thyroidectomy or x-radiation, that a low BMR was not always associated with a high blood cholesterol level, and that elevated blood cholesterol concentration was not always associated with clinical evidence of myxedema. He concluded that unexplained hypercholesterolemia points more specifically to thyroid deficiency than does a low basal metabolic rate, and that the relationship between the blood cholesterol level and the BMR is usually reciprocal when a change has occurred or has been imposed in a patient's thyroid status. Thus, he thought the blood cholesterol concentration might be used as a guide during treatment of certain thyroid disorders. Others reported that cholesterol levels can be "normal" in both hypothyroidism and hyperthyroidism[55] and that cholesterol levels are often a poor guide in hyperthyroidism[56,57]; but most noted that cholesterol concentrations are usually elevated in hypothyroidism.[55-58] The degree to which the blood cholesterol level is elevated in hypothyroidism has been related to the patient's euthyroid cholesterol level,[58,59] but not necessarily to the degree of thyroid deficiency.[59] Over-all, the clinical evidence is against the notion that the basal metabolic rate and the blood (or plasma) cholesterol level are necessarily inversely related. The demonstration by Cutting, Rytand, and Tainter[60] that dinitrophenol increases the rate of basal oxygen consumption without reducing the blood cholesterol level strongly supports this conclusion.

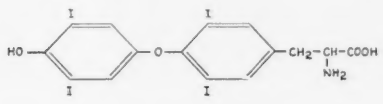
Elevation of phospholipids without change in the ratio of cholesterol to phospholipid has been reported in hypothyroidism.[55,58,61] It has been said that there is no consistent increase in circulating lipids other than cholesterol in hypothyroidism but that treatment reduces the levels of phospholipids and neutral fat, as well as of free and ester cholesterol.[62] (A reduction in all these lipids has been produced in euthyroid and even in hyperthyroid patients by the daily intravenous injection of sufficiently large doses of L-T_3.[63]) There is agreement that β-lipoprotein cholesterol is lowered by L-T_3.[63-65] The finding that L-T_3 (in small doses) and certain thyroxin analogues increase α-lipoprotein cholesterol[64,65] is less well confirmed. The detailed effects of desiccated thyroid, L-T_4 and L-T_3, on the patterns of serum lipoproteins determined by ultracentrifugation have been extensively investigated.[66-68] Thyroactive compounds can also affect unesterified fatty acids; sharp increases in serum levels after single intravenous injections of L-T_3 have been observed.[69]

EFFECTS OF THYROID HORMONES ON CIRCULATING LIPIDS

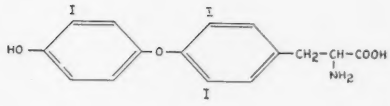
Extensive reviews concerned with the thyroid hormones are available.[70-73] Only a brief comparison of pertinent physiologic activities will be made here. L-T_4 and L-T_3 (Fig. 2) are the compounds that will be considered thyroid hormones.

L-Thyroxin and L-T_3.—

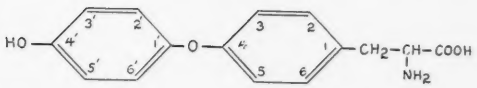
Very soon after L-T_3 was discovered it was shown to be about 5 times more



3,5,3',5'-Tetraiodothyronine
Thyroxin (T_4)



3,5,3'-Triiodothyronine (T_3)



Thyronine

Fig. 2.—The structural formulas of the thyroid hormones, L-T_4 and L-T_3, and the ring-numbering convention shown on the thyronine formula. These formulas can represent both the L and the D isomers.

potent than L-thyroxin by goiter-prevention test in rats,[73a] and a comparable potency difference for the treatment of hypothyroidism in man was quickly demonstrated. Daily intramuscular doses of 0.08 mg. caused clinical improvement, the BMR rising and the serum cholesterol level falling to normal.[74] Elaborate metabolic studies comparing L-T_3 with L-T_4 established that the new hormone is as effective as the old one in the treatment of myxedema in human beings.[75-78] Asper and associates[75] injected these hormones subcutaneously and reported that serum cholesterol concentrations decreased more quickly after 0.5 to 1.0 mg. of L-T_3 than after 0.6 to 4.8 mg. of L-T_4, and that changes in cholesterol were not quantitatively related to the BMR effects. Giving the same compounds orally, Selenkow and Asper[76] noted no difference in the degree or rate of change of serum cholesterol levels following calorigenically equivalent doses. (They found the daily oral doses needed to maintain treated cases of myxedema in a euthyroid state to be 0.075 to 0.105 mg. of L-T_3 and 0.300 mg. of L-T_4.) Rawson and co-workers[77] found a prompt but short-lived increase in the BMR after L-T_3, and a slow and prolonged rise after L-T_4. They thought the differences in speed of action were quantitative, not qualitative, and were correlated with the rate at which these hormones disappeared from the circulation. Kyle and associates,[78] when they gave large single doses of sodium L-T_4 (2 to 3 mg. orally),

$L\text{-}T_3$ (1 mg. subcutaneously), and desiccated thyroid (1,200 to 1,500 mg. orally), failed to find differences in rapidity and duration of action as judged by heart rate, BMR, nitrogen excretion, and serum cholesterol effects. However, Beierwaltes and Ruff[79] gave healthy euthyroid men increasing doses of either sodium $L\text{-}T_4$ (up to 2 mg. daily) or $L\text{-}T_3$ (up to 0.525 mg. daily) for 17 days, produced the expected rise in BMR and fall in cholesterol level, but found differences in the persistence of these changes between the $L\text{-}T_4$ and $L\text{-}T_3$ groups. Two days after $L\text{-}T_3$ was stopped, the cholesterol level had already risen and the BMR fallen, the former reaching its base line in 10 days and the latter in 6. For $L\text{-}T_4$, the cholesterol level continued to fall through the second posttreatment day, was stable for 2 more days, then gradually rose to the base-line level over 2 to 3 weeks. The BMR followed the same pattern, rising for 2 days after $L\text{-}T_4$ was stopped, beginning to fall 2 days later, and reaching its base line between the tenth and twenty-second posttreatment days.

EFFECTS OF SOME THYROXIN ANALOGUES

The closely related derivatives and the isomers of $L\text{-}T_4$ and $L\text{-}T_3$ are often referred to simply as thyroxin analogues. Many have been tested by one or more bioassays in laboratory animals, and some of these have been given to human beings. There are several general reviews,[70,80-82] many comparative in vitro and small animal in vivo experiments,[83-89] and some comparative reports of clinical experiences.[90-93] The analogues listed in Table I were selected as representative of stereoisomers, of alterations in the alanine side chain, and of varied patterns of iodination. Included are most of the analogues which have been widely investigated in man since the recognition of $L\text{-}T_3$. To keep the survey of appropriate length, analogues formed by substitutions of the hydroxyl or of the ether oxygen groups and those with ring substitutions other than iodine were arbitrarily excluded.

The D Isomers of T_4 and T_3.—

Because of the asymmetric middle-carbon atom of the alanine side chain, all thyronines can exist in D and L stereoisomeric forms. The natural thyroid hormones are the L isomers and are more potent than the D. $D\text{-}T_4$ has been studied rather extensively by bioassay in animals and in human beings.[94] It is relatively more potent in rats in depressing cholesterol levels than in stimulating oxygen consumption, compared with $L\text{-}T_4$ and with many other analogues.[86-89] This may also be true in human beings, for certain doses will lower the serum cholesterol without raising the BMR in myxedema[95] and in euthyroidism,[96] but the dose needed to sustain serum cholesterol depression is variable and may be high enough to precipitate angina pectoris in some patients with coronary heart disease.[97] Insignificant effect on the serum cholesterol level in noncalorigenic doses has been reported.[98]

$D\text{-}T_4$ has been shown to have about one tenth of the calorigenic effect of $L\text{-}T_4$ in man.[99,100] It has been used to treat myxedema, the maintenance dose being given variously as 10 times that of $L\text{-}T_4$,[101] as 10 mg. daily,[96] and as 8 mg.

daily.[100] The minimum daily oral dose that would lower serum cholesterol levels was found to be 2.5 mg. in hypothyroid patients and 7.5 mg. in euthyroid patients,[64] but considerable individual variation exists. Apart from thyromimetic effects, few side reactions to D-T_4 have occurred. However, there is one report that it increased prothrombin time in patients who were receiving Dicumarol.[102]

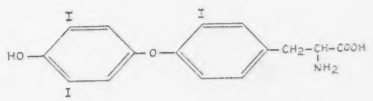
It does appear that D-T_4 has a rather more potent cholesterol-lowering effect than has L-T_4 in doses that are equivalent calorigenically. This may be due, at least in part, to differences in distribution of the isomers among the body tissues. Tapley and co-workers[103] showed that in rats D-T_4 disappeared from the blood more rapidly than L-T_4 and was concentrated to a greater extent in the liver and kidneys and to a lesser extent in the brain, muscle, and skin. In human beings, too, D-T_4 disappeared from the blood more rapidly.[104,105] Other studies in man showed differences in the metabolic disposition of the D and L isomers of both thyroid hormones and suggested that D-T_4 and D-T_3 may undergo metabolic transformation in the body.[106]

Much less has been published about D-T_3. Studies of rats have demonstrated that D-T_3 has a relatively greater cholesterol-lowering potency than its L isomer at doses which caused equivalent stimulation of the heart rate[88] and prevention of goiter.[86,87] In hypothyroid patients a daily dose of 0.2 mg. caused an 18 per cent decrease in serum cholesterol levels without change in the BMR, but 0.5 mg. daily, while decreasing the serum cholesterol level 29 per cent, caused an increase in the BMR of 8 per cent.[64] The same investigators estimated the approximate daily dose of D-T_3 needed to lower the serum cholesterol level to be 0.2 mg. in hypothyroid and 0.5 mg. in euthyroid patients. No specific data on maintenance dosage were found, but a study with DL-T_3* of 12 hypothyroid patients established an average maintenance dose of 0.147 mg.[106a] Studies in euthyroid patients establish that D-T_3 is a potent cholesterol-lowering agent,[64, 107-109] but it is capable of causing angina pectoris in some patients with coronary heart disease even in the absence of an elevation in the BMR.[64]

Close interpretation of data on the D isomers is made difficult in some cases by uncertainty about the degree to which the materials tested were contaminated with the more potent L isomers.

L-T_2 and D-T_2.—

Diiodothyronine (T_2), iodinated in the 3,5 positions (Fig. 3), is a thyroactive compound of lesser potency than T_4 or T_3. The L isomer is more potent than the D. D-T_2 causes a relatively greater depression of serum and liver cholesterol concentrations and a relatively lesser stimulation of heart rate in rats



3,3',5'-Triiodothyronine (3,3',5'-T_3)

Fig. 3.—The formula of 3,5-T_2.

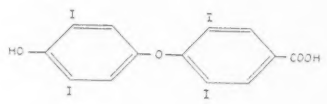
*This is the racemic form of 3,5,3'-triiodothyronine (a mixture of equal parts of the D and L isomers).

than L-T_2.[88] Given to patients with hypothyroidism, daily oral doses of 3 mg. and of 9 mg. of L-T_2 caused, respectively, 22 and 40 per cent reductions in serum cholesterol and 4 and 14 per cent increases in the BMR. The approximate minimum oral daily dose at which L-T_2 lowered serum cholesterol levels was found to be 3 to 5 mg. in hypothyroid patients and 10 to 15 mg. in euthyroid patients. Daily oral doses of D-T_2 of 50 mg. and 80 mg. given to hypothyroid patients reduced serum cholesterol levels by 22 and 38 per cent, respectively. The smaller dose did not change the BMR, but the larger elevated it by 20 per cent. The approximate daily oral dose of D-T_2 needed to depress serum cholesterol levels was 50 to 75 mg. in hypothyroid patients and 150 to 200 mg. in euthyroid patients. L-T_2 at a dose of 10 to 15 mg. a day produced effort angina in 3 of 6 susceptible men. D-T_2, however, at daily dosage of 200 mg. caused no angina in 7 men with coronary heart disease.

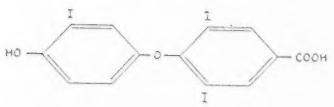
All of the above information concerning L-T_2 and D-T_2 in clinical trials comes from the extensive studies of Boyd and Oliver.[64,92]

The Formic Acid Analogues of T_4 and T_3.—

Changing the side chain of thyroxin from alanine to formic acid results in a thyroactive compound of greatly decreased potency. Lacking an asymmetric carbon, it cannot exist in more than one stereoisomeric form. Formulas of the formic acid analogues are shown in Fig. 4.



3,5,3',5'-Tetraiodothyroformic Acid (Tetraform)



3,5,3'-Triiodothyroformic Acid (Triform)

Fig. 4.—The formulas of "Tetraform" and "Triform."

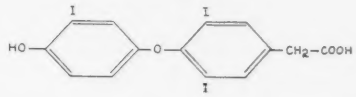
Tetraform has a relatively greater effect in bioassays in rats on cholesterol metabolism than on goiter prevention,[86,87,110,111] stimulation of oxygen consumption,[112] or stimulation of heart rate.[88] In man the approximate daily oral dose required to depress serum cholesterol levels is 100 mg. in hypothyroidism[64] and 200 to 400 mg. in euthyroidism.[64,108] These large doses contain enough iodine to have caused skin, salivary gland, and gastrointestinal symptoms of iodism in some patients.[93]

There is relatively little information about 3,5,3′-triiodothyroformic acid.

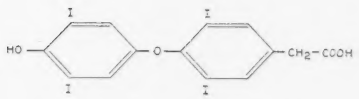
It is inactive in human myxedema in doses up to 20 mg. daily.[113] Several rat bioassay studies are available.[86,87,89]

The Acetic Acid Analogues of T_3 and T_4.—

Triac (Fig. 5) was the first analogue to be synthesized and extensively studied after the discovery of T_3, and it provided impetus to later studies of other compounds. One reason it has held such interest is that theoretically it can be a natural metabolite of the thyroid hormones.



3,5,3'-Triiodothyroacetic Acid (Triac)



3,5,3',5'-Tetraiodothyroacetic Acid (Tetrac)

Fig. 5.—The formulas of the acetic acid analogues of T_3 and T_4.

Triac was not outstanding for cholesterol-lowering potency in the comparative studies of rats referred to previously. When it was given to patients with myxedema, however, there was appreciable lowering of serum cholesterol level without elevation of the BMR,[114,115] or with relatively less elevation of the BMR than was produced by L-T_4.[116] More detailed metabolic studies of patients with myxedema confirmed the possibility of the fall in cholesterol levels with little or no rise in BMR,[117-119] but failed to show a clear difference between Triac and T_3 or T_4.[117,120] The separation of oxygen consumption–stimulating and cholesterol-depressing effects appeared to be a function of dosage, possible with daily oral doses of Triac up to 1.0 mg.,[64] or 1.5 mg.[118,121] in myxedema. With doses of 4 mg. a day, the BMR rose to normal.[121] Euthyroid status was achieved with 6 mg. a day.[122] Carefully documented studies of patients with hypothyroidism who were given single oral doses of 12 mg. of Triac showed a rise in the BMR by the fourth hour and a fall in serum cholesterol levels within 6 to 18 hours, maximal (about 15 per cent below the base line) at 24 hours. Three patients with myxedema and histories of previous angina were reported to have developed ischemic symptoms when treatment was begun with Triac.[121]

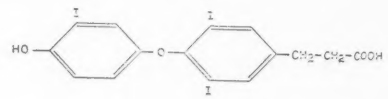
In euthyroid patients no significant changes were found in circulating lipids until the daily oral dose reached 3 mg. At 4 mg. a day, unsustained depression of serum cholesterol of 21 per cent was noted with a reduction in β-lipoprotein cholesterol and a rise in α-lipoprotein cholesterol, but no significant change in the BMR.[65,123] In another study, this dose was found to elevate the BMR about 10

per cent, on the average, though some patients had a decrease in serum cholesterol level without an increase in the BMR.[123a] The fall in β-lipoprotein cholesterol was reported by others,[124] but the rise in α-lipoprotein cholesterol was not confirmed.[124,125] Angina pectoris was produced by Triac at doses of 3 to 5 mg. daily in 2 of 12 men with euthyroidism and coronary heart disease even though the basal metabolic rates were not raised.[123] Caution has been advised in the treatment of patients with coronary artery disease with Triac.[121,123]

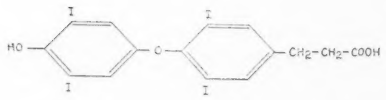
Tetrac (Fig. 5) has been studied much less extensively. Clinical remission in myxedema has been reported with daily doses of 8 mg. (with a fall in cholesterol before a rise in the BMR),[126] and with daily doses of 9 mg. (with a fall in the cholesterol level without a rise in the BMR only at doses below 4 mg. a day).[122] Metabolic effects of Tetrac are similar to those of the thyroid hormones, but this analogue is considerably less potent.[117]

The Propionic Acid Analogues of T_3 and T_4.—

In comparative bioassays in rats Triprop (Fig. 6), like Triac, had no unusual effects on the metabolism of cholesterol, but in man it has been found to show the same kind of separation of cholesterol-lowering and oxygen consumption–stimulating effects at low doses that were mentioned before for other compounds.[91,127,128] It has been under investigation a shorter time than Triac and fewer detailed studies have been published.



3,5,3'-Triiodothyropropionic Acid (Triprop)



3,5,3',5'-Tetraiodothyropropionic Acid (Tetraprop)

Fig. 6.—The propionic acid analogues of T_3 and T_4.

In a patient with hypothyroidism a daily oral dose of 0.6 mg. was found to reduce the serum cholesterol level, the BMR not rising until the dose was raised above 2 mg. a day.[122] The largest daily dose which will not elevate the BMR in hypothyroidism varies from patient to patient, reported between 1 and 4 mg. a day,[128-130] depending, it seems, on how rapidly the dose is raised, how long the patient has been on the dose, and how severe the hypothyroidism is. There is some difference of opinion about the daily oral maintenance dose for full replacement therapy of myxedema. It has been estimated at 2 to 2.5 mg. with a range of 1 to 4 mg.,[129] at 2.5 mg. with a range of 1.25 to 5,[91] and at 3 to 6 mg. daily.[127,128]

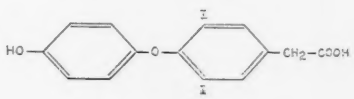
With gradually increasing doses, the serum cholesterol level has been reported to fall more rapidly than the BMR rises, and when full euthyroid status has been reached the per cent of fall in cholesterol level has been proportional to the height of the original (hypothyroid) cholesterol level, at least for original cholesterol levels above about 200 mg. per 100 ml.[127,130] Patients with myxedema who have histories of angina pectoris tolerated doses of Triprop varying from 1 to 4 mg. a day without increase in angina and often with improvement in it.[129] The onset of action of Triprop is rapid and the dissipation of its effects occurs quickly,[91] the time relationships approximating those of L-T_3 rather than L-T_4. This, combined with a lesser tendency than have thyroid hormones to elevate the BMR or to produce angina pectoris,[91,129] suggests that Triprop may have special usefulness in treating patients with heart disease who have been made myxedematous and hypercholesterolemic by thyroid ablation for severe angina or cardiac failure. Not enough data have yet been published to settle this point. Except for reactions expected of a thyroactive compound, very few side effects have been noted. Urticaria has been reported.[128] Slight diarrhea sometimes is produced. In patients susceptible to angina, the therapeutic margin is more favorable than it is with desiccated thyroid.[129]

Euthyroid patients tolerate Triprop well and respond with a fall in serum cholesterol which averages 20 per cent.[127,131,132] Phospholipids, total esterified fatty acids,[127] and β-lipoprotein cholesterol[133] all fall quite consistently. The BMR tends to rise as the dose is increased, but it stays within the euthyroid range a doses of 4 to 6 mg. a day.[130]

There are few clinical data available on Tetraprop (Fig. 6). One myxedematous patient required 12 to 14 mg. daily for maintenance replacement dosage.[122] The minimum dose needed to lower cholesterol in euthyroid patients has been given as 3 to 6 mg.[131] Prolonged administration to euthyroid men failed to lower β-lipoprotein cholesterol.[133]

The Acetic Acid Analogue of T_2.—

Diac (Fig. 7) was found to exhibit marked dissociation of cholesterol-lowering and calorigenic effects in bioassays in rats[89] and this encouraged its clinical trial. When given orally to hypothyroid patients in daily doses of 50 mg. or 80 mg., the respective depressions of serum cholesterol levels were 14 and 35 per cent, and the increases in BMR 2 and 18 per cent. The approximate daily oral dose that would reduce the serum cholesterol content in these patients with hypothyroidism was 50 mg., and for those with euthyroidism, it was 150 mg.



3,5-Diiodothyroacetic Acid (Diac)

Fig. 7.—The formula of Diac.

None of the hypothyroid or euthyroid patients developed angina.[64] Some studies[134,135] showed an interesting effect not noted with the other analogues discussed. There was little change in cholesterol levels in patients taking doses of Diac up to 30 or 50 mg. a day, but the BMR was depressed quite regularly and distinctly. As the dosage of Diac was increased to the range of 100 mg. a day, depression of serum cholesterol levels became definite and calorigenic effects were observed. Thus, Diac at certain doses acted in a direction opposite to the action of the thyroid hormones. This may be partly, but is not likely mainly, an iodide effect.

3,3′,5′-Triiodo-DL-Thyronine.—

A rather large number of analogues are thyroxin antagonists,[80] but 3,3′,5′-T_3 is especially interesting. It has been spoken of as a thyroid hormone[136] and its metabolism has been studied after injection in rats[136] and in man.[137] The closeness of its structural relationship to 3,5,3′-T_3 deserves mention (Fig. 8).

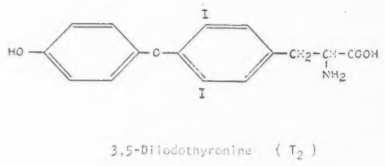


Fig. 8.—The formula of 3,3′,5′-T_3. Though this compound closely resembles the natural hormone, 3,5,3′-L-T_3, it is not thyroactive.

Given in large doses to untreated hypothyroid patients, 3,3′,5′-T_3 is inactive,[130,138] but it can cause temporary partial remission of hyperthyroidism, including a decrease in the BMR and a transient rise in the serum cholesterol level.[130,139]

That the effect in hyperthyroidism is not due entirely to released iodide is strongly suggested by studies of Pittman, Barker, and co-workers.[138,140] They showed that the injection of 3,3′,5′-T_3 into thyroidectomized rats receiving calorigenic doses of L-T_4 depressed the BMR to the base-line hypometabolic level.[140] In 3 of 4 hypothyroid patients who were treated respectively with maintenance doses of L-T_3, L-T_4, and desiccated thyroid, the administration of large doses of 3,3′,5′-T_3 depressed the BMR to hypothyroid levels.[141] Therefore, it appears that 3,3′,5′-T_3 inhibits some peripheral actions of L-T_3 and L-T_4. Little has been reported about effects on cholesterol levels.

DISSOCIATION OF EFFECTS OF THYROID HORMONES: CHOLESTEROL VERSUS BMR

There is much evidence for the concept of dissociation of thyroid hormone effects by structural alterations of the T_4 and T_3 molecules.[142] In the case of cholesterol versus BMR, this is by no means a new idea. Peters and Man[57] pointed out in 1950 that when myxedema is treated serum cholesterol levels respond more rapidly than other criteria of thyroid activity and may return to normal before the BMR or serum precipitable iodine has been appreciably affected. The weight

of reported clinical observations and metabolic studies supports the idea that the effects of administered thyroid hormones or analogues on the metabolism of cholesterol are independent of certain other effects, such as over-all calorigenic action or direct myocardial "toxicity." For the thyroid hormones and for most of the analogues reviewed, it has been possible to find a dose which, when given to untreated hypothyroid patients, will cause a fall in the serum cholesterol level before, or, perhaps, in some cases without, causing a detectable elevation of the basal metabolic rate.

Whether or not this is observed may depend more on the design of the study than on the hormone or analogue studied (although differences between analogues in this regard do seem to exist). The frequency of measurement of the BMR and cholesterol level after the test compound is started or stopped, the amount of the starting or final dose, and the frequency and increment of change in dose, all can profoundly influence the clinical demonstration of this "dissociation." For example, giving large doses of a thyroactive compound and making observations only infrequently might provide data the graph of which would resemble Fig. 9. But starting with small doses, slowly increasing them by small increments, and measuring the BMR and cholesterol level frequently and regularly could result in a graph more like Fig. 10, in which there is a space of time during which the serum cholesterol concentration has fallen appreciably before the BMR has begun to rise. Other kinds of time relationships are, of course, possible with different experimental designs, different compounds, and different patients.

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THE USE OF THYROXIN ANALOGUES IN MYXEDEMA

The role of thyroxin analogues in the therapy of hypothyroidism has been limited. Desiccated thyroid (of reliable potency), L-thyroxin and L-T_3 are all satisfactory drugs to use in uncomplicated myxedema.[143-145] However, there may well be a place for one or more of the analogues in special cases, such as those made hypothyroid in an effort to relieve intractable angina pectoris or cardiac failure. There is no proof that the hypothyroid patient develops atherosclerosis at an accelerated rate,[146] so the risk he faces from his associated hypercholesterolemia is unknown. But the risk associated with hypercholesterolemia in the euthyroid population is becoming clearer and more impressive as new data accumulate.[147,148] If one should consider it important to treat the hypercholesterolemia of iatrogenic myxedema, as well as the unpleasant hypothyroid symptoms, and if the conventional replacement drugs should, for some reason, not be satisfactory, then there are adequate indications for the trial of one of the analogues.

Difficulties in using thyroactive compounds in patients with coronary heart disease have arisen, but there is little doubt that serum cholesterol levels have been reduced. Unfortunately, there is no substantial evidence that reducing the blood cholesterol level benefits euthyroid patients who have already developed sufficiently severe disease to have angina pectoris. Those who are still free of heart disease, who may tolerate thyroactive compounds quite well, are the ones to whom hypercholesterolemia may be most threatening. Drugs, such as some thyroxin analogues, which may help reduce cholesterol safely, must be considered,

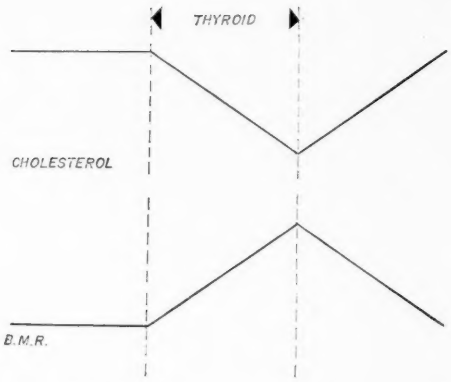

Fig. 9.—Diagrammatic representation of cholesterol-BMR relationships under certain hypothetical conditions (see text). In this situation "dissociation" is not demonstrated. The abscissa is time. (From Transactions and Studies of the College of Physicians of Philadelphia, 1961.[150])

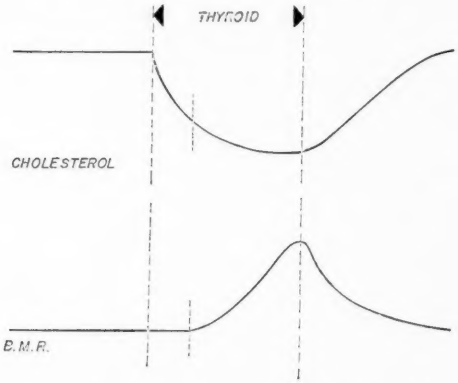

Fig. 10.—Diagrammatic example of "dissociation" of the cholesterol-lowering and BMR-elevating effects of a thyroactive compound under certain hypothetical conditions (see text). The abscissa is time. (From Transactions and Studies of the College of Physicians of Philadelphia, 1961.[150])

along with control of nutrition, as potentially useful in reducing the risk associated with hypercholesterolemia.

SUMMARY

Knowledge of the metabolism of cholesterol in conditions of deranged function of the thyroid gland has been reviewed, and clinical correlations between serum lipids, basal metabolic rate, and thyroid status surveyed. The effects of the thyroid hormones, L-thyroxin and 3,5,3′-triiodo-L-thyronine (L-T_3) on circulating lipids, particularly in hypothyroidism, were summarized. They were compared with the following thyroxin analogues: D-thyroxin and 3,5,3′-triiodo-D-thyronine (D-T_3); 3,5-diiodo-L-thyronine (L-T_2) and D-T_2; 3,5,3′,5′-tetraiodothyroformic acid (Tetraform) and 3,5,3′-triiodothyroformic acid (Triform); 3,5,3′-triiodothyroacetic acid (Triac) and 3,5,3′,5′-tetraiodothyroacetic acid (Tetrac); 3,5,3′-triiodothyropropionic acid (Triprop) and 3,5,3′,5′-tetraiodothyropropionic acid

(Tetraprop); 3,5-diiodothyroacetic acid (Diac); and 3,3′,5′-triiodo-DL-thyronine (3,3′,5′-T_3). Except for 3,3′,5′-T_3, which appears to antagonize some thyroid hormone effects peripherally, these analogues are thyroactive to greater or lesser degrees. Their cholesterol-lowering potency has been compared with other actions, and the significance of apparent dissociation of cholesterol-lowering and calorigenic effects has been assessed. Therapeutic implications have been briefly explored.

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THYROIDITIS AND HYPOTHYROIDISM

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THAT certain patients with thyroiditis exhibit signs and symptoms of hypothyroidism has been recognized for many years. These are particularly characteristic of the later stages of the form of chronic thyroiditis described by Hashimoto in 1912 (struma lymphomatosa, lymphadenoid goiter, or Hashimoto's disease), of which the dominant clinical feature is a notably hard and enlarged thyroid gland. The revelation that Hashimoto's disease was associated with a high degree of autoimmunity to thyroid protein,[31] together with the experimental demonstration of autoimmune thyroiditis,[32] has been responsible for a considerable renewal of interest both in thyroiditis and in its relationship to other thyroid diseases, particularly to the more common syndrome of hypothyroidism without thyroid enlargement—so-called idiopathic (nongoitrous) myxedema. Although more questions have been raised by these discoveries than have yet received definite answers, the unresolved problems of the etiology and pathogenesis of ordinary hypothyroidism have been provided with a new and interesting perspective.

THYROIDITIS AND THYROID AUTOIMMUNITY

The term "autoimmunity" implies production within the organism of antibody to one or more of its normal native constituents. In 1956, striking evidence was obtained by Roitt, Doniach, Campbell, and Hudson[31] that such a process was occurring in patients with Hashimoto's disease. The initial demonstration depended on formation of a visible precipitate when the patient's serum was allowed to react with a saline extract of human thyroid gland, indicating a serum precipitating antibody to some constituent of the extract. The latter was identified as thyroglobulin, the hormone-storing protein of the colloid.[30] Serum antibody levels were high in recent, untreated patients and accounted for the gamma globulin elevation and deranged "liver function" tests which had already been observed in patients with lymphadenoid goiter.[6,14] After thyroidectomy, however, the precipitin reaction became weaker or disappeared altogether.[8] That true *auto*immunity was concerned was proved when the specific reaction was obtained between a patient's serum and an extract of her own thyroid tissue.[42]

These original observations have now been confirmed and extended in several directions. Boyden's tanned red-cell principle[4] has provided a much more sensitive method of detecting thyroglobulin antibody than the precipitin test, and has enabled quantitative estimation of antibody levels.[26,28,43] A second antibody has been identified in many cases, directed against an intracellular substance associated with the microsomal fraction of thyroid extracts, which can be detected by complement-fixation methods.[3,28,36] The antigen concerned is present in abundance only in thyrotoxic glands and is probably related to functional thyroid activity. It is likely that still other antigen-antibody systems may operate: there is, for example, some evidence of a second antigen in the colloid, distinct from thyroglobulin.[29] A so-called "cytotoxic factor" can be demonstrated in Hashimoto sera, which inhibits the early growth of human thyroid cells in tissue culture.[27] This substance, which is now known to be thermostable and to require the presence of complement for its effect,[23] may be an autoantibody to an unidentified component of the thyroid cell membrane.

ROLE OF AUTOIMMUNITY IN PATHOGENESIS

The possible implications of the foregoing have received much attention, but the exact part played by autoimmunity in the pathogenesis of Hashimoto's disease has not yet been finally agreed upon. It was originally postulated that some initial, possibly minor, injury to thyroid tissue allowed thyroglobulin to escape from the follicles, wherein under normal conditions it is strictly confined. Since the body on that account treated it as a "foreign" protein, antibody formation ensued, and by causing additional thyroid damage initiated a self-perpetuating cycle which would ultimately result in total thyroid destruction. An increasing tendency to deficiency of circulating thyroid hormone led to pituitary stimulation and compensatory thyroid hyperplasia under the influence of thyrotropin. The patient's clinical state of thyroid function would reflect the net result of the opposing factors and might at first be well compensated, although myxedema would eventually supervene.

This attractive hypothesis has required some modification in the light of the subsequent demonstration that thyroid autoimmunity may sometimes be a limited and temporary process. The transient appearance of thyroglobulin antibody in the blood has been described following acute mumps thyroiditis,[13] whereas low-titer antibodies have been noted in other thyroid diseases not associated with progressive autoimmunity of the Hashimoto pattern.[28] Unless some individuals are abnormally liable to develop a chain reaction between antibodies and thyroid tissue, it must be assumed that whatever is responsible for exposing the potential antigens imitates an artificial immunization schedule in acting repetitively or over a long time. The nature of this factor is still uncertain (see below), but to it must be conceded the leading role in etiology.

This is not to deny the importance of autoimmunity in determining the pattern of both structural and functional disturbance, for which there is compelling experimental evidence. Rabbits immunized against their own thyroid tissue not only produce circulating autoantibodies but develop histologic changes

in the portion of the gland left in situ which bear a striking resemblance to those of human chronic thyroiditis,[32,41] and, as long ago as 1942, it had already been observed that rabbits which developed antibody against their own thyroglobulin following immunization with the human variety became slowly and progressively myxedematous over the course of about 6 months.[24]

AUTOIMMUNITY IN HYPOTHYROIDISM WITHOUT GOITER

During the original serologic studies in Hashimoto's disease, it became apparent that precipitating thyroglobulin antibody was not entirely specific to that condition but was also found in occasional patients with ordinary myxedema without goiter.[8,15,36] Application of the very sensitive tanned cell agglutination method to the thyroglobulin system allowed detection of antibody in much smaller concentration and amplified this finding. Circulating antibody proved to be present little or no less often in authenticated cases of primary myxedema than in Hashimoto's thyroiditis: the difference lay in the generally much lower serum concentrations, which were in most cases less than that required for a positive precipitin reaction. The distribution of antibody levels in a group of myxedematous patients closely resembled that found among surgically treated or long-standing inactive cases of Hashimoto's disease.[26]

Subsequent studies, including tests of skin sensitivity to intradermal thyroid extract,[5] have confirmed the immunologic similarity between the two clinical syndromes. Irvine[23] has recently reported a significant titer of the Hashimoto "cytotoxic factor" in 11 of 14 patients with nongoitrous myxedema. The findings are consistent with the suggestion of Doniach and Roitt[8] that myxedema may be an end stage in the thyroid autoimmune reaction and lend strong support to the view that Hashimoto's disease and idiopathic myxedema represent variants of the same fundamental pathologic process. The difference in clinical manifestation, if it is not due to varying interaction between autoimmunization and other, as yet unidentified, etiological factors, may merely reflect the ability of the anterior pituitary to stimulate thyroid enlargement and so postpone the threatened hormone deficiency. In ordinary myxedema the phase of thyromegaly either fails to occur, perhaps because compensatory adjustment is outpaced by tissue destruction or else passes unnoticed by the patient. It is interesting to note that intermediate syndromes, in which myxedema is associated with a small but firm and easily felt gland, are being recognized increasingly often.[7,21] The unknown variable determining clinical pattern may in some way be related to sex, since the classical Hashimoto reaction occurs almost exclusively in females, whereas nongoitrous myxedema, although it has a marked predilection for that sex, affects also a fair proportion of men (about 20 per cent of the cases).

HISTOLOGIC CONSIDERATIONS

Under the microscope, the Hashimoto goiter is dominated by generalized and dense infiltration with lymphocytes and plasma cells. Characteristically, there is also enlargement and oxyphilia of the follicular epithelium and occasional giant cells replace colloid within the follicular lumina (see for example, Hazard[20]).

Fibrosis occurs, but is variable in degree. It is likely that autoantibody, at least to thyroglobulin, is formed within and around the thyroid gland itself rather than in remote areas of the reticuloendothelial system, and that the round cell infiltration is in fact an invasion by active antibody-producing elements of the immune defences. Evidence in support of this view has been obtained from nodular and toxic goiters, a proportion of which show similar lymphadenoid changes, although here they are focal and of low grade: the presence of such areas in a series studied recently showed a high correlation with thyroglobulin antibody in the circulation.[33] "Autoimmune thyroiditis" seems justified as an accurate and functional description of this type of histologic change. The intense, universal reaction characteristic of Hashimoto's disease is very different in degree from the limited and nonprogressive change sometimes seen in other goiters and is paralleled in the blood by very much higher levels of circulating antibody. The level, however, drops sharply if most of the affected tissue is removed by thyroidectomy.

Opportunities for pathologic study of the gland remnant in nongoitrous myxedema have been much less frequent. But histologic examination of specimens removed at autopsy have usually revealed, in addition to fibrotic replacement of the parenchyma, residual changes of chronic thyroiditis somewhat similar (except in volume and intensity) to Hashimoto's disease. These consist of focal accumulations of lymphocytes and plasma cells, metaplasia of residual follicular epithelium, and sparse, poorly staining colloid occasionally associated with multinucleated giant cells.[1,9]

THE CONCEPT OF AUTOIMMUNE THYROIDITIS

Histologic evidence thus supports the idea of a basic unity between Hashimoto's disease and myxedema. Since positive serologic tests are obtained with sufficient frequency to implicate autoimmunity as a constant and integral feature of both conditions, they may justifiably be regarded as varieties of "autoimmune thyroiditis"—provided that this term is not taken to imply that autoimmunity is their primary cause.

The relationship of thyrotoxicosis to autoimmune thyroiditis is still being studied. Clinically, symptoms of hyperthyroidism are common at the outset of Hashimoto's disease, and an appreciable proportion of patients with thyrotoxicosis, if untreated, eventually become myxedematous.[11] Between one and two thirds have been shown to have thyroid autoantibody in the circulation, usually of low titer,[28,34] and this is paralleled by focal lymphadenoid changes in surgical specimens examined after thyroidectomy.[33] At least during the usually short present-day periods of observation without treatment, the autoimmune process remains limited and nonprogressive[28] and clinical transition into Hashimoto's disease or myxedema is rare. But that autoimmune thyroiditis, even of this low grade, may be of functional importance is suggested by the relationship which has been established between histologic lymphoid infiltration and postthyroidectomy hypothyroidism.[17,40] The presence of thyroglobulin antibody in the serum confers a similar liability to myxedema, both after operation[34] and after treatment with radioactive iodine.[2]

RELATIONSHIP TO OTHER TYPES OF THYROIDITIS

It seems to be generally true that the association of hypothyroidism with thyroiditis is confined to the autoimmune variety, apart from rare instances of total thyroid destruction by an inflammatory process and artificial radioiodine ablation of the gland for therapeutic reasons. Thus, the subacute or "creeping" thyroiditis of de Quervain, a self-limiting disease of unknown etiology, does not appear to provoke thyroid autoimmunity[7] nor does it result in hypothyroidism.[20] This is in marked contrast to the occasional cases of frank autoimmune thyroiditis which run an acute or subacute course, where serum antibody levels are high and in which myxedema may develop with remarkable rapidity.

The relationship of Riedel's thyroiditis (struma fibrosa) to Hashimoto's disease has been controversial for many years and is still not clear. At least some cases to which the former label has been attached have been shown on serologic investigation to be examples of autoimmune thyroiditis, supporting the early view of Ewing[12] that Riedel's struma was a later and more fibrotic stage of struma lymphomatosa.

ETIOLOGY

The nature of the thyroid injury which must be presumed both to precede and to accompany the development of progressive autoimmunity has not been ascertained. The probability that it results in the liberation of thyroglobulin from the follicles is supported by the detection of an abnormal iodine-containing protein in the serum of some patients with Hashimoto's disease.[25] For reasons given above, it seems unlikely that virus infection is responsible. One suggestion is that hyperthyroidism comes first, overstimulation of thyroid tissue by the pituitary being responsible for antigen release and the subsequent immune response. Primary hyperthyroidism would thus sometimes be modified by autoimmunity into the syndrome of chronic thyroiditis, perhaps representing a crude attempt at self-cure. This would explain the frequency with which toxic symptoms precede Hashimoto's disease,[37] the presence of serum autoantibody in many thyrotoxic patients, and the occurrence of transitional histologic patterns between classical thyrotoxicosis and lymphadenoid goiter.[16]

Alternatively, the primary defect may reside in the thyroid gland itself. The basement membrane of the follicular epithelium, which normally insulates the potentially antigenic material from the extracellular environment, has been shown to be deficient in autoimmune states,[35] although this change may be secondary to the action of a humoral or other injurious agent or even to the autoimmune process itself. An intriguing possibility is that an abnormality of the thyroglobulin, or a defect in the enzymes which normally break it down, is responsible for its liberation in an antigenic form.

Wherever the lesion and whatever its nature, evidence accumulates that it may be genetically determined. Familial examples of myxedema are far from infrequent,[22,38] and classical Hashimoto's disease has also been recorded in families.[10,34] Striking evidence suggesting genetic predisposition to thyroid autoimmunity was recently obtained by Hall and his co-workers[18] on investigating the

relatives of propositi with frank autoimmune thyroiditis: approximately half the siblings studied showed significant titers of thyroid antibodies, many without clinical evidence of thyroid disorder. The results of serologic tests in other relatives were consistent with dominant Mendelian transmission of the tendency to thyroid autoimmunity. The high incidence of thyroid antibodies among relatives of patients with thyroiditis has been confirmed by Doniach in a personal communication (1960). The findings suggest that the defect which permits autoimmunization is genetic in origin, and show in addition that autoimmune thyroiditis may often occur without clinical expression, or at least may clearly precede such expression. This may explain why the hereditary pattern displayed by the clinical syndromes is not more obvious. The site and nature of the transmitted abnormality await additional investigation, but it is of interest that the familial occurrence of an abnormal iodine-containing protein in the circulation has been recently reported.[39]

SUMMARY AND CONCLUSIONS

Recent work relevant to the relationship between thyroiditis and hypothyroidism is reviewed. Autoimmunity to thyroglobulin and other normal thyroid constituents is a constant feature both of Hashimoto's thyroiditis and of primary, nongoitrous myxedema, and in both of these the histologic changes in the thyroid probably reflect invasion of the gland by elements of the immunity system. There is thus some justification for regarding them as variants of the same basic pathologic process, "autoimmune thyroiditis." Whereas autoimmune thyroiditis tends to be associated with progressive hypothyroidism, other types of thyroiditis do not. Minor and apparently nonprogressive autoimmune reactions sometimes occur in thyrotoxicosis but, even here, there is evidence of an association with hypothyroidism. Progressive autoimmune thyroiditis is likely to be the result of long-continued or repetitive exposure of the potentially antigenic components of thyroid tissue. The factor responsible is unknown but may well be genetic in origin.

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THE DIAGNOSIS AND TREATMENT OF PRIMARY AND SECONDARY HYPOTHYROIDISM

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THE clinical features of hypothyroidism have not changed since they were originally described by Gull in 1874[1] and summarized so well by the Clinical Society of London in 1888.[2] Yet it is extraordinary how frequently the diagnosis is missed and that patients may suffer from their symptoms for years before the true nature of the disorder is recognized. This is attested by the fact that in recent years cases of myxedema coma are being reported in increasing frequency although this state was described in 1888. Since the symptoms and signs of hypothyroidism may be reversed by proper replacement therapy with thyroid hormone, it is imperative to recognize the condition when a patient presents himself. As in the case of many diseases, the most common cause of failure to diagnose hypothyroidism is a lack of a high index of suspicion on the part of the physician. Furthermore, patients with myxedema* frequently have such an impaired memory that an adequate and complete history cannot be obtained. Once a euthyroid state has been restored, the patient may then give a far better description of the time of onset and character of his previous symptoms. In such a situation the original physical examination may be more informative than the history in arriving at the correct diagnosis.

ETIOLOGICAL FACTORS

Conditions predisposing to the development of hypothyroidism are listed in Table I. When the thyroid gland fails to develop or becomes destroyed in utero, the child is born with hypothyroidism and is known as a cretin. It has recently been suggested, although not proved, that thyroid failure before birth may be due to an autoimmune mechanism.[3] For a full discussion of cretinism and juvenile hypothyroidism, the reader is referred to the excellent text by Wilkins.[4] Hypothyroidism with goiter may be due to inherited defects in reactions leading to hormonal synthesis, of which several have been recognized[5,6]: (1) trapping of iodide by the thyroid cell, (2) oxidation of iodide to molecular iodine, (3) iodination of tyrosine, (4) coupling of iodinated tyrosines to form triiodo-

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*For the most part, recent literature has been reviewed. For references to original or earlier work the reader should consult previous reviews or texts. The term, myxedema, implies advanced hypothyroidism with myxedematous infiltration of the tissues.

thyronine or thyroxine, (5) deiodination of iodotyrosines, and (6) formation of an abnormal iodinated compound other than thyroxine or triiodothyronine which has very little calorigenic activity. There may be failure of proper development of the thyroid when it is in an aberrant position; patients with lingual goiter[7,8] may be hypothyroid or euthyroid and may first present with local symptoms of a strawberrylike mass at the base of the tongue. Dietary deficiency of iodine rarely leads to hypothyroidism; in the adult in areas of endemic goiter, it is usually seen only in older people.[9] Certain foodstuffs, such as cabbage and rutabagas, contain a goitrogen which interferes with thyroid hormone synthesis[10] and, if consumed in sufficient quantities, may lead rarely to the development of goiter and hypothyroidism.[11]

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TABLE I. CONDITIONS CONTRIBUTING TO HYPOTHYROIDISM

1.	Congenital absence of the thyroid
2.	Defects in hormonal synthesis
3.	Aberrant lingual thyroid
4.	Dietary iodine deficiency
5.	Foodstuffs containing goitrogens
6.	Idiopathic atrophy of the thyroid
7.	End result of prolonged untreated hyperthyroidism
8.	Thyroidectomy—operation or I^{131}
9.	Pituitary insufficiency
10.	Chronic thyroiditis
11.	Drugs—antithyroid, PASA, cobalt, iodides, SCN, resorcinol

The type of hypothyroidism seen most commonly in middle-aged women and described by Gull[1] has been termed idiopathic since the etiology is unknown. However, the occurrence of thyroid antibodies in such patients is almost as high as in those with Hashimoto's disease[12]; it has been postulated, therefore, that the thyroid may have been altered previously by an autoimmune process and that atrophy then supervenes. Idiopathic myxedema is usually recognized toward the end of the fifth decade or early in the sixth decade of life in an approximate sex ratio of 80 per cent females to 20 per cent males, and with an incidence of 0.06 to 0.08 per cent of hospital admissions.[13,14]

There are a few instances recorded where myxedema has occurred as an end result in patients with untreated hyperthyroidism over a long period of time.[13] The appearance of hypothyroidism after surgical thyroidectomy is variously reported to be from 1 to 20 per cent, with the larger number of cases found in children or when the operation is performed for chronic thyroiditis.[15-17] Hypothyroidism occurs after therapy of hyperthyroidism with radioiodine in 5 to 15 per cent of patients.[18-21] After either operation or I^{131} therapy, the hypothyroidism may develop in a few months and be of a temporary nature [18,20]; symptoms may last one to two months and then the patient returns spontaneously to a euthyroid state when the remaining functional thyroid tissue responds to stimulation by endogenous thyrotropin. The true incidence of permanent hypothyroidism after surgical thyroidectomy or I^{131} may be higher than is generally reported since the

condition may develop from a few months to several years following therapy.[19] Ideally, all patients so treated should be followed at intervals for the rest of their lives and be observed for the possible development of hypothyroidism.

Hypothyroidism may ensue as part of the general syndrome of panhypopituitarism,[22] or together with gonadotropin deficiency,[23] or as a result of thyrotropin deficiency of the pituitary alone[24,25] ("secondary" hypothyroidism). Hypothyroidism rarely follows acute or subacute thyroiditis[26] but is a common sequel of lymphocytic thyroiditis.[27] The most likely diagnosis in an adult with a goiter and hypothyroidism is chronic thyroiditis of the Hashimoto type. This disorder is now thought to be due to a gradual destruction of the thyroid gland by an antibody-antigen reaction as demonstrated by the presence of antibodies to thyroglobulin in the serum.[12] Hypothyroidism may also accompany Reidel's struma. Carcinoma of the thyroid and systemic diseases involving the thyroid rarely induce enough destruction of the gland to produce hypothyroidism.

Numerous drugs have been implicated in the development of hypothyroidism. Overtreatment of hyperthyroidism with antithyroid drugs may lead to temporary hypothyroidism which will revert to euthyroidism when therapy is discontinued, even though the patient may have taken the drug for several years. Euthyroid patients who have been receiving thyroid hormone may become temporarily hypothyroid for a few weeks after stopping the medication before the suppressed gland resumes its function.[28] Instances of goiter and hypothyroidism have been reported in patients with tuberculosis who are being treated with para-aminosalicylic acid.[29] This drug acts in a manner similar to that of the thiouracil drugs by impairing hormonal synthesis. Since there are many thousands of patients being treated with para-aminosalicylic acid for tuberculosis, and only a few develop hypothyroidism, such patients must have a basic defect in the thyroid gland which is made manifest by the administration of the drug. There have been reports of patients treated for anemia with preparations of cobalt who acquired goiter and hypothyroidism[30]; the mechanism of action of cobalt in retarding thyroid hormone synthesis has not been clarified.[31] In recent years several patients have exhibited hypothyroidism following the administration of excessive amounts of iodide, particularly for asthma.[32,33] The excess iodide apparently imposes a block at an undetermined site in the chain of reactions leading to synthesis of thyroid hormone. These patients probably have a predisposing defect which is accentuated by iodide since innumerable patients with asthma receive potassium iodide as therapy for many years. Euthyroidism is usually re-established after the medication is discontinued. Thiocyanate and resorcinol have been implicated in precipitating hypothyroidism.[34,35] Finally, hypothyroidism has been induced by administration of radioiodine as a therapeutic measure in patients with intractable angina pectoris, congestive heart failure, and pulmonary emphysema. The rationale of such a procedure in emphysema is highly questionable since patients with myxedema have reduced maximal breathing capacity and diffusing capacity, and alveolar hypoventilation.[36]

CLINICAL FEATURES

The onset of hypothyroidism is so insidious that the patient may be unaware

that anything is amiss. It is often members of his family or friends who urge him to seek medical advice. The common symptoms and signs of hypothyroidism, such as weakness, lethargy, dry skin and hair, puffy eyes, paresthesias, hoarseness, constipation, and cold intolerance are well known. Some of them occur in euthyroid older people with significant frequency so that hypothyroidism may be suspected.[37,38] The characteristic facies is one which is puffy, expressionless at rest, pale, slightly yellow, at times showing a malar flush; comparison with photographs taken previously may be striking. The patient often has an untidy appearance. Means[13] and Lloyd[39] have described changes in the voice and speech which are pathognomonic of myxedema. The voice is husky with a low pitch and an increased catarrhal or nasal quality and a clotted quality as if the mouth were full of chocolate; the speech is slow and deliberate with difficulty in articulation and slurring of groups of words. The patients may complain that they can no longer sing with the same pitch. These changes are probably due to myxedematous infiltration of the lips, tongue, and larynx. Asher[40] quotes a patient who was told she was like an old toad; our most recent patient with myxedema was a middle-aged lady who said,"I do not know what is the matter with me; I sound like an old goose." Deafness is a common symptom of hypothyroidism and this is usually perceptive in type[41]; deaf-mutism may be associated with hypothyroidism.[42]

Hypothyroidism induces significant changes in the functions of the cardiovascular system.[43] The pulse rate is not necessarily slow. The blood pressure may be low or normal, but hypertension is not infrequently observed. Low voltage in the electrocardiogram is a helpful sign. The cardiac output is low and increases with exercise, in contrast to that of patients in congestive heart failure of other etiology; hemodynamic studies in hypothyroidism suggest that the enlarged heart is due to pericardial effusion rather than cardiac dilatation.[44] The relationship of hypothyroidism and arteriosclerosis is still unclear.[45]

Alterations in the function of the central nervous system are probably more widespread than usually recognized.[46] Loss of memory, mental lethargy, and complacency are common. Murray has found that the reaction time is lengthened in most hypothyroid patients.[47] Headache, auditory hallucinations, psychosis, tinnitus, and vertigo may be present; convulsions which have disappeared on therapy have been reported.[48] The misdiagnosis of a brain tumor has been made.[49] A cerebellar syndrome with ataxia, unsteadiness, and clumsiness has been described.[50] Paresthesias may occur in a high proportion of patients with hypothyroidism[51]; these may be due to peripheral neuropathy or to the carpal tunnel syndrome from pressure of accumulated myxedematous tissue. Retardation of the relaxation of the deep tendon reflex responses due to an abnormal contractile mechanism of the muscle may be a valuable sign[52]; Lawson has recently demonstrated that impairment in the contractile phase of the tendon reflex can be measured and that a delay in this response may be an indication of early hypothyroidism.[53]

Constipation may in some cases be due to actual enlargement of the colon as demonstrated by roentgen examination.[54] Diminished tone of the bladder and gall bladder has also been found.[55,56] Although a few female patients have amenorrhea, the majority have menorrhagia[51,57]; not infrequently a dilatation and curettage

or even a hysterectomy is performed for prolonged menstrual bleeding when the true cause was not recognized. Myalgia and arthralgia may be sufficiently severe that the patient first seeks medical advice because his movements are limited.[51]

Although myxedema coma was mentioned by the Clinical Society of London in 1888[2] and by Hertoghe in 1911,[58] this subject has received scant attention until recently. In the past 7 years, more than 40 cases have been reported[59]; this is probably the result of a renewed awareness of the condition rather than an increased incidence. The patients are seen in a stuporous or comatose state with the classic symptoms and signs of myxedema. Hypothermia with temperatures ranging down to 75° F. is characteristic, although elevation of temperature has been noted.[60] Most of the cases have been discovered during the winter months. The patient appears like a corpse with occasional respirations indicating that he is still alive. The skin is actually cold. The time from the onset of illness to coma and death is usually 10 to 15 years although shorter intervals have been reported; death is due in most cases to a superimposed infection or to pulmonary, cardiac, or renal complications. Narcosis from retention of carbon dioxide may play a role in the fatal outcome.[61]

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PITUITARY HYPOTHYROIDISM

In their classic studies on hypopituitarism, Sheehan and Summers[22] detected a well-marked atrophy of the thyroid gland in many cases and in some of these there was extensive fibrosis. With loss of stimulation by thyrotropin from the pituitary, hypothyroidism supervenes. Peters and associates[23] found that subsequent to destruction of the anterior pituitary from any cause, gonadal failure occurred first, followed by thyroid deficiency; adrenocortical function was the last to be affected. There may, however, be variations in the sequence of events. Hypothyroidism develops within 4 to 8 weeks following surgical hypophysectomy.[62]

Although the typical picture of full-blown myxedema may accompany hypophyseal insufficiency, symptoms and signs of hypothyroidism are less prominent as a rule than when there is primary thyroid failure. Patients with pituitary hypothyroidism lose rather than gain weight; the alterations in the skin are less marked; it may be dry, but is usually not as coarse. Loss of axillary and pubic hair is more prominent with pituitary deficiency. The cardiac silhouette is small rather than large. Amenorrhea is present rather than menorrhagia because of lack of gonadotropin; a history of a postpartum hemorrhage or shock may be valuable in differential diagnosis.[22] However, Fraser and Garrod[63] have reported 4 cases of primary thyroid failure and myxedema subsequent to postpartum shock. Evidence of adrenal insufficiency may also be present, including postural hypotension and hypoglycemia. In the male with hypopituitarism, atrophy of the testes and prostate is present. A history of visual disturbance and the finding of impaired visual fields to color and an enlarged sella turcica by roentgen examination suggest the presence of a tumor of the pituitary. Patients with far-advanced pituitary insufficiency may lapse into coma which may be very difficult to distinguish clinically from primary myxedema coma.[64]

LABORATORY EXAMINATIONS

Anemia associated with hypothyroidism is usually normocytic but may be macrocytic[65]; it has been attributed to impaired synthesis of erythrocytes in the bone marrow,[66] to reduced absorption of vitamin B_{12} from the gastrointestinal tract,[67] or to a shortened life span of the erythrocytes.[68] Low serum iron and decreased iron-binding capacity have been found. The erythrocytic sedimentation rate may be elevated without the presence of infection, and may not be related to the degree of anemia.[51,69] The view has long been held that proteinuria occurs in hypothyroidism. However, in a recent review of 15 cases, 10 patients failed to show proteinuria, and of the 5 in whom it was present, 4 had hypertension and one had chronic pyelonephritis.[70] In another series of 66 patients, 12 had proteinuria, but in only 4 of these could the proteinuria be attributed to hypothyroidism in the absence of renal disease.[51] It is rather questionable, therefore, that proteinuria is a constant feature of hypothyroidism without other renal disease. Serum total proteins may be increased as a result of elevated beta globulins.[71] Cerebrospinal fluid protein may be increased even to high levels without other apparent disease of the central nervous system.[46,72,73] Concentrations of serum electrolytes are usually normal in hypothyroidism, whereas hyponatremia would be indicative of pituitary hypothyroidism. However, hyponatremia has been reported in advanced primary myxedema.[74] Fasting blood sugar is normal in primary myxedema but may be low in pituitary hypothyroidism. The serum cholesterol is commonly elevated in primary hypothyroidism, but in such patients with poor nutrition it may be within the normal range.[14] In pituitary hypothyroidism, the serum cholesterol is usually normal, but many cases have been seen with elevated values.[23] The serum uric acid has been found elevated in males and older females with hypothyroidism in the absence of gout or renal disease.[75]

In spite of more recent procedures using the serum protein-bound iodine (PBI) concentration and radioactive iodine, the basal metabolism test is still of much diagnostic value, expecially in the cases in which exogenous iodine invalidates the results of the former tests.[76] A low basal metabolic rate, when determined under conditions which are really basal, may indicate hypothyroidism but does not differentiate between primary and pituitary failure. The level of the serum PBI is a very accurate index of thyroid function provided that the patient is not receiving therapy with thyroid hormone and has not been given any form of exogenous iodine in the preceding few weeks. In cases where the excess iodine is in the inorganic form, a butanol extractable iodine (BEI) level can obviate this difficulty.[77] However, if the iodine has been administered in an organic form, such as certain dyes used for radiography, both the PBI and the BEI are spuriously elevated and may remain so for many months.[78,79] The serum PBI is also elevated during pregnancy because of an excess of circulating thyroxine-binding protein.[80] Recently, a patient has been described who had a deficiency of thyroxine-binding globulin; the serum protein-bound iodine level was 2.0 μg per cent and yet there was no clinical evidence of hypothyroidism and other tests of thyroid function were normal.[81]

The use of radioactive iodine has greatly facilited diagnosis of disorders of thyroid function. Most commonly, the per cent I^{131} uptake by the thyroid gland

in 6 hours and 24 hours following an oral tracer dose is used in North America, whereas the 2 hour I^{132} uptake is employed in Great Britain.[82] Measurement of urinary excretion of radioiodide or of the rate at which radioiodine appears in the serum protein-bound iodine fraction can also be utilized. In a clinical appraisal of tests with I^{131} and serum PBI, McConahey, Owen, and Keating[83] found the uptake of I^{131} in 6 hours and 24 hours and the serum PBI to be of greatest value in the diagnosis of hypothyroidism. The I^{131} uptake may be depressed if the patient has received therapy with thyroid hormones, iodine compounds, or many other substances.[84] The administration of thyrotropic hormone (TSH) has been of much assistance in distinguishing primary from pituitary hypothyroidism.[85-87] Since TSH exerts its maximum effect 18 to 24 hours after administration,[88] it is usually given as a single intramuscular dose of 4 to 10 units on the day before the patient receives the radioiodine. A significant increase in the 24 hour I^{131} uptake is indicative of potentially normal thyroid function and suggests pituitary insufficiency. On the other hand, no response to TSH designates primary thyroid failure. If pituitary insufficiency has been of long duration, with subsequent marked atrophy of the thyroid, there may be no response to TSH even when it is administered for several days. A positive test with TSH, therefore, in the absence of interfering substances, indicates pituitary hypothyroidism, but a negative one does not necessarily exclude it.[89,90] Another laboratory procedure which is helpful, particularly when the PBI and the I^{131} tests are invalid, is a measure of the uptake of I^{131}- labeled triiodothyronine by erythrocytes in vitro.[91,92] This test depends upon the amount of thyroid hormone bound to serum protein and has been interpreted as a measure of the concentration of free thyroid hormone in the circulation.[93] A low uptake of I^{131}-triiodothyronine by red cells is suggestive of hypothyroidism, but can also be seen in other conditions, such as pregnancy.

The ability to excrete a water load is impaired in pituitary insufficiency, but is usually normal in primary hypothyroidism[90,94]; however, delayed excretion of water which was not corrected by cortisone has been reported in primary hypothyroidism.[95] The urinary 17-ketosteroids are depressed in both types of thyroid failure. Plasma 17-hydroxycorticosteroids are normal in primary hypothyroidism and usually low in pituitary insufficiency, where production of ACTH is lacking; urinary 17-hydroxycorticosteroids may be low in primary as well as in pituitary hypothyroidism.[90,96] Pituitary reserve as tested by SU 4885 is normal in primary hypothyroidism, but diminished in pituitary insufficiency.[97,98] The urinary excretion of FSH in patients with primary hypothyroidism may be as low as 6 mouse units, and occasionally may be zero; in pituitary insufficiency it may be zero or may be only partially lowered.[90,99] This test, therefore, cannot be relied upon in differentiating between primary and pituitary hypothyroidism.

DIFFERENTIAL DIAGNOSIS

It is far more common for hypothyroidism to be diagnosed incorrectly as some other condition rather than for a diagnosis of hypothyroidism to be made when it is not really present. The pallor, macrocytic anemia, and gastric achlorhydria may suggest pernicious anemia. When myxedema is present, congestive

heart failure or the nephrotic syndrome may be suspected; in the latter condition the serum PBI may be depressed.[100] Myalgia and arthralgia may masquerade as fibrocytis, neuritis, or arthritis. Menorrhagia due to hypothyroidism has been frequently diagnosed as functional uterine bleeding. Disease of the central nervous system may be suggested by headache, convulsions, stupor, coma, and a high cerebrospinal fluid protein. Some patients with far-advanced hypothyroidism are found in mental institutions because of psychoses. A careful history and physical examination together with appropriate laboratory tests will differentiate primary hypothyroidism from these conditions.

When a patient develops hypothyroidism following a thyroidectomy or therapy with radioiodine, the symptoms and signs may not be so striking as in idiopathic hypothyroidism. Jefferies and associates[101] have described low thyroid reserve in patients who have had partial destruction of the thyroid gland by thyroidectomy, I^{131} therapy, thyroiditis, and in some cases of nontoxic goiter. This has been demonstrated by variable responses in I^{131} uptake and serum PBI to administration of TSH; such patients may have mild symptoms and signs of hypothyroidism.

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TREATMENT

Treatment of hypothyroidism involves simply supplying what the patient's thyroid gland cannot make for him. The first patient treated with an extract of sheep's thyroid reported upon by Murray[102] in 1891 lived for almost 30 years. Replacement therapy leads to complete alleviation of the symptoms and reversal of the metabolic alterations to a euthyroid state. The patients, of course, need to be treated for the rest of their lives. It is most important to inform members of the family of this fact since patients frequently feel so well that they stop taking thyroid and slowly lapse into hypothyroidism again. The proper dosage level is best estimated by the clinical appearance and the sense of well-being of the patient. In older patients and in those who have a history of heart disease, it is wise to start with a small dose and increase at weekly intervals until the full replacement amount has been attained. Patients with coronary insufficiency may develop angina pectoris when their metabolic rate is increased; the dose of the drug can be raised only to a level commensurate with a lack of cardiac symptoms so that all features of hypothyroidism may not be abolished. In younger patients with uncomplicated hypothyroidism, the full replacement dose can be initiated immediately.

Desiccated thyroid has been well standardized now and is still the cheapest preparation available in the United States. The usual daily dose required for maintenance of euthyroidism is about 120 mg.; older patients may feel perfectly well with 60 mg. daily; a few patients need 180 mg. daily. If symptoms are not alleviated and a patient seems to require more than 180 mg. daily, the original diagnosis of hypothyroidism should be questioned and the situation reviewed again.

It is possible that tablets of desiccated thyroid lose potency on standing or may become very hard and not properly absorbed in the gastrointestinal tract.

Synthetic crystalline sodium l-thyroxine is a pure compound, is uniformly potent, and is the preparation of choice; cost of the drug should be the only deterrent to its use. The usual maintenance dose of this compound is 0.2 to 0.3 mg. daily. The use of triiodothyronine as standard replacement therapy is unnecessary; however, in cases of myxedema coma where a rapid effect is desired, triiodothyronine should be employed. The proper dose for patients in myxedema coma has not yet been determined; many of these patients have had a fatal outcome whether they received small or large amounts of triiodothyronine.[103] It would seem reasonable to give 50 μg intravenously every 12 hours at first, and then increase the dose if the patient does not respond or if he does not have a history of coronary disease. Such patients may need therapy with norepinephrine to sustain blood pressure, and hydrocortisone if there is some question that the coma may be on the basis of hypopituitarism.

When desiccated thyroid is employed as maintenance therapy, the level of the serum PBI may aid in determining the proper dosage. When thyroxine is used, however, the serum PBI may be above the normal range when the patient is euthyroid; with the use of triiodothyronine, the PBI may remain in the hypothyroid range even though the patient is euthyroid.[104] The administration of other analogues of thyroxine or of triiodothyronine does not seem warranted for standard replacement therapy since they have less calorigenic activity and larger doses are necessary. Since the maximum effect from a single dose of desiccated thyroid or thyroxine is not reached for several days, the patient will need to take his full replacement dose only once daily. There is some evidence that the output of thyroid hormone from the gland and the peripheral utilization of hormone by the tissues may be altered in certain states of stress[105-107]; however, almost all patients do quite well on a constant daily dose without having the need to alter it.

In patients with mild or partial hypothyroidism, a full replacement dose of thyroid is usually obligatory; a small dose would serve to suppress the partially functioning thyroid gland and the patient would still remain deficient in circulating thyroid hormone. A few years ago a syndrome of metabolic insufficiency was described; these subjects had certain of the symptoms encountered in hypothyroidism together with a somewhat low basal metabolic rate. Other laboratory tests of thyroid function were normal. The patients were found to respond to triiodothyronine but not to thyroxine or desiccated thyroid.[108,109] It was postulated that there was a defect in the conversion of thyroxine to triiodothyronine in the peripheral tissue cell. However, there have been two recent reports of carefully conducted double-blind studies which revealed that such patients responded just as well to a placebo as to triiodothyronine.[110,111] Therefore, it is very doubtful that the syndrome of metabolic insufficiency is a distinct entity, and therapy with triiodothyronine is not justified.

The patient with pituitary hypothyroidism, of course, will need replacement therapy with cortisone and testosterone or estrogen as well as with thyroid, depending on which pituitary hormones are deficient. Actually when a patient with hypothyroidism does not respond properly to adequate doses of thyroid hormone, pituitary insufficiency may be present. It has been reported that therapy

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with thyroid without cortisone may induce an adrenal crisis; Peters and coworkers[23] have discounted this claim and have found the BMR and serum PBI to be restored to normal without ill effects with thyroid when the doses are gradually increased. However, to attain maximum well-being, these patients should receive cortisone, the dosage of which may need to be increased during stressful situations, and testosterone or estrogen; in the postmenopausal woman, therapy with estrogen is unnecessary.

Therapy with desiccated thyroid, thyroxine, or triiodothyronine is also used as a suppressive measure in patients with diffuse or nodular goiters, thyroid cancer, chronic thyroiditis, lingual goiter, and as a diagnostic test for hyperthyroidism.[112-116] There does not seem to be any other rational use for therapy with thyroid hormones. The long-held view that infertility and multiple abortions are due to some degree of thyroid deficiency has recently been discounted except in patients with proved hypothyroidism.[117,118] Likewise, thyroid has been used injudiciously in the treatment of obesity; it has been demonstrated that patients with far-advanced hypothyroidism gain only about 6 to 15 pounds in weight.[14,51] The great majority of obese persons do not have hypothyroidism; low basal metabolic rates found in such people are often within the normal range when corrected for ideal height and body weight. Therapy with thyroid hormones, therefore, is unwarranted.

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THE HEART IN HYPOTHYROIDISM

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A SIGNIFICANT relationship between the heart and the state of the thyroid gland was indicated by early clinical observations of altered cardiovascular function in patients with hyperthyroidism or myxedema. The fundamental influence of the hyperthyroid state on cardiovascular status has gained widespread acceptance since Parry's[1] original description of exophthalmic goiter in 1786, recorded as a form of heart disease in 1825. A comparable, specific effect of the hypothyroid state on the heart was suggested by the pathologic and anatomic studies of Ord[2] in 1880 and the clinical descriptions of Zondek[3] in 1918 and Fahr[4] in 1926. These authors, particularly Fahr, evolved the concept of "myxedema heart," implying functional inadequacy of the heart caused by the hypothyroid state and based on the observations in markedly myxedematous subjects of "dilatation of the heart, slow indolent heart action, a normal blood pressure, low electrocardiographic complexes, and essentially complete reversability of the abnormalities following thyroid administration."

It would not be practicable to review, in detail, the large and rapidly expanding body of literature which has resulted from recent advances in our knowledge of thyroid and cardiac physiology and biochemistry, the continuing improvement in diagnostic techniques which has extended greatly the scope of hypothyroidism, and the vast upsurge of interest in the interrelationship of atherosclerosis, cardiovascular disease, and thyroid function. This report, therefore, deals with selected aspects of the relationship between hypothyroidism and the heart, including signs and symptoms, pathogenetic mechanisms, diagnosis, the induction of hypothyroidism for the treatment of certain forms of heart disease, and the relationship of thyroid function to atherosclerosis. The problem of therapy will not be considered in detail as it is treated elsewhere in this symposium.

SIGNS, SYMPTOMS, AND PATHOGENETIC MECHANISMS

Heart Size and Pathologic Changes.—The heart or, more strictly, the cardiac

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silhouette, has generally been described as increased in size in cases of marked myxedema. The increase has been attributed to (1) dilatation attendant upon atony, (2) true hypertrophy, (3) interstitial edema, (4) fibrous tissue replacement, and (5) associated pericardial effusion, or to varying combinations of these elements. However, in an extensive experience with euthyroid patients rendered myxedematous by radioactive iodine for the therapy of severe angina pectoris or intractable congestive failure, it has been observed[5] that there has been no increase in cardiac size when small doses (1/10 to 3/4 grain) of desiccated thyroid are given daily to produce a controlled hypothyroid state. Definitive pathologic data on the state of the heart in untreated hypothyroidism are meager. In a series of 20 autopsies recorded by the London Clinical Society in 1888,[6] the heart was examined in 9 instances and was considered abnormal in only 2. One of these exhibited an early stage of interstitial myocarditis and the other a comparatively advanced stage of the same process. Also noted was some thickening of the adventitia of the arterioles. In subsequent scattered individual reports on advanced cases coming to autopsy, the heart has been described as "flabby," pale, and dilated, with some hypertrophy of the cardiac musculature. A conspicuous change has been fibrous tissue replacement or infiltration which is not distinguishable from findings in patients with progressive coronary artery disease. Other microscopic findings, most of which are also nonspecific, have included swelling of the muscle cells—some pale while others are deeply stained with small pyknotic nuclei, vacuolization, degeneration of muscle fibers with relative loss of transverse striations in favor of longitudinal striations, occasional fatty infiltration, and interstitial edema—accumulation of faintly basophilic staining material in large, irregular vacuoles which are brilliantly P.A.S. positive.[7] Similar changes have been described by Webster and Cooke[8] in experimental hypothyroidism in rabbits. The precise chemical nature of the interstitial fluid has not been determined but it is characterized as mucinous, with a high protein and nitrogen content, akin to the mucopolysaccharide of the ground substance. Brewer[9] suggests two different types of mucoid deposition because of his failure to demonstrate an effect of hyaluronidase. Thus, the pathologic changes are, in large measure, nonspecific and their evaluation most difficult because of the almost universal attendant complications of old age, atherosclerosis, hypertension, diabetes, or other cardiovascular diseases.

The statement that atherosclerosis occurs prematurely and with greater intensity in myxedematous or cretinous subjects is widely scattered throughout the literature. The classic report of the committee of the Clinical Society of London, based on an extensive investigation of myxedema, failed to report arterial degeneration of any of the larger vessels. A more recent series[10] of 10 largely untreated cases describes a significant degree of coronary atherosclerosis in each one, but the age of the patients ranged from 62 to 78 years, a period in life when "spontaneous" atherosclerosis is almost universally present. Our own data[11] and a critical review[12] of the evidence relating thyroid hormone, cholesterol metabolism, and coronary atherosclerosis raise provocative questions concerning the validity of the widely assumed causative interrelationship. It seems clear

that the relation of hypothyroidism to atherosclerosis in the adult requires further documentation. Although cases have been reported of marked atherosclerosis in cretins and in juvenile patients with myxedema, such findings, which would offer the strongest evidence of an etiological relationship, are by no means universal. While supporting experimental data on this subject are voluminous, critical evaluation leads us to conclude that the roles of hypothyroidism and its attendant hypercholesterolemia in the pathogenesis of atherosclerosis remain to be clarified.

Of correlative interest are 3 cases of induced hypothyroidism in relatively young people with hypertension, followed by spontaneous rupture of the aorta with chromatotrophic degeneration of the muscular coat similar to the idiopathic, cystic, medial necrosis of Erdheim.[13] It is noteworthy, however, that, in a personal experience totaling over 300 cases of surgically or I^{131}-induced hypothyroidism, not a single instance of rupture of the aorta has been observed[14]; nor has this been reported in a nationwide experience of over 1,300 cases.

It is further essential, in the evaluation of any primary cause-and-effect interrelationship between hypothyroidism and cardiovascular derangements, to consider that such correlations have been based almost wholly on studies in severe, long-standing myxedema. Recent studies have indicated significant secondary effects of long-standing myxedema on other bodily functions, particularly those of other endocrine organs. Thus, the contribution of other endocrine changes remains to be assessed. In addition, improvements in the sensitivity, accuracy, and specificity of diagnostic methods[15] have broadened the concept of hypothyroidism to include milder and earlier cases in which no evidence of heart abnormality is found. Taken together, these considerations indicate the need for a critical reappraisal of the pathogenetic role of the hypothyroid state in cardiovascular disease before long-standing gross myxedema supervenes.

Circulatory Dynamics.—The total picture is generally described as an adynamic one.[16] The heart action is sluggish with feeble pulsations on fluoroscopic examination. The heart sounds are generally muffled or distant, probably related to diminished contractile force and the frequently associated pericardial effusion. The pulse is characteristically slow but may be rapid and instances of arrhythmias (paroxysmal auricular tachycardia, extrasystoles, complete or incomplete heart block, Stokes-Adams syndrome) have been described. The blood pressure is generally normal but may be decreased or increased. It is noteworthy that some cases of increased blood pressure have been reported with a return to normal following adequate therapy of the hypothyroidism.[17] The velocity of blood flow is strikingly slowed in virtually all cases of myxedema, in general proportionately to the decrease in basal metabolic rate.[18] The total peripheral blood flow is decreased, probably as a result of the striking reduction in flow of blood through the skin.[16] The blood volume and plasma volume are both decreased, returning to normal with replacement therapy.[19,20] The total peripheral vascular resistance of the body has been calculated to be increased.[21]

The cardiac output is significantly decreased in myxedema, mainly because of a decreased stroke volume.[22] Stewart and associates[23] found values by the acetylene method of 1.95 L. per minute or 26.3 c.c. per beat in a myxedematous

subject which increased on thyroid replacement therapy to 3.41 L. per minute and 42.6 c.c. per beat, respectively. Scheinberg and co-workers, [21] using the direct Fick method, found a mean decreased cardiac output of 47 per cent, correlating with a mean decrease in total oxygen consumption of 37 per cent. They noted an excellent correlation between the cardiac index and the basal metabolic rates.

The important issue is whether the reduction in cardiac output is a manifestation of myocardial insufficiency. Ellis[24] observed that, despite the lowered cardiac output, the peripheral venous and right auricular pressures were not increased. In 2 patients with myxedema subjected to exercise, they observed an increase in total cardiac output, but only at the price of a definite increase in the mean pulmonary arterial pressure. In studies in 12 myxedematous subjects,[22] the reduced cardiac output was associated with normal to slightly elevated pressures in the right atrium, pulmonary artery, and brachial artery. During exercise, there was an increase in brachial and pulmonary arterial pressure with a striking decrease in peripheral resistance and no change in pulmonary resistance. It was suggested that these pressure changes and the diastolic dip in the right ventricular pressure tracings reflect the limitations of diastolic filling associated with pericardial effusion and corroborate that heart failure is not present. On the basis of the striking increase in arteriovenous oxygen difference, Stewart[23] concluded that the heart in myxedema does not maintain adequate circulation, even for the lowered metabolic requirements. However, Schaub,[7] who found a similar increase in A-V oxygen difference, concluded that this is due not to inadequate cardiac performance, but rather to the marked slowing of peripheral blood flow (especially through the skin), resulting in more marked desaturation of the returning blood. Scheinberg[21] noted a moderate increase above normal in the mixed A-V oxygen difference but found that this was not statistically significant. They found that the arterial oxygen saturation was below normal in 4 of 8 patients. When measured in 8 other patients, the mean arterial oxygen saturation of hemoglobin was reduced from a normal of 97 to 93 per cent and the mean calculated arterial oxygen tension from a normal of 100 mm. Hg to 71 mm. Hg. They postulated that the arterial oxygen unsaturation might be caused by inadequate pulmonary ventilation or by changes in the alveoli or capillary wall. It is worthy of note that cerebral blood flow and cerebral oxygen consumption were both decreased to the same extent in myxedema, so that the cerebral A-V difference was not altered. Similarly, renal blood flow has been shown to be decreased about proportionately to the decreased level of metabolism.[25]

In the careful hemodynamic study of 12 hypothyroid patients in Campbell's[22] laboratory, the resting cardiac index was below normal in all, but increased normally with exercise. Moreover, the cardiac output: oxygen consumption ratio was not significantly different at rest from that during exercise. The decrease in basal cardiac output was primarily attributable to a decrease in stroke volume in the presence of a low normal heart rate; on exercise, the rise in output was primarily by an increase in stroke volume. The mean A-V difference did not differ significantly from normal. These data on resting and response to exercise were thus quite different in hypothyroidism from those in congestive failure. The consensus is that the circulatory dynamics in man are so nearly normal in relation

to the oxygen consumption in myxedema that it seems unnecessary to postulate cardiac insufficiency.

The experimental studies of Brewster and his colleagues[26] are in accord with this view. They showed in lightly anesthetized hypothyroid dogs that initial myocardial tension was essentially the same as in euthyroid or hyperthyroid animals. However, the duration of the contracted state and the time required for muscle relaxation were significantly longer in the hypothyroid animals as compared to the other two groups. The changes observed in these parameters in response to changes in bodily temperature were the same in the three groups studied. Mean right and left atrial pressures were slightly higher, while end diastolic ventricular pressures were unchanged in the hypothyroid animals as compared to the euthyroid or thyroid-fed dog. Balourdas, Croll, and Scott,[27] studying the effects of hypothyroidism on the heart in dogs, have shown a comparable reduction (about 25 to 30 per cent) in cardiac output, coronary sinus blood flow, left ventricular oxygen consumption, left ventricular work, and heart rate; however, left ventricular efficiency and coronary vascular resistance were increased. Atropine produced an increase in all these values in the normal dog and in the hypothyroid animal. Since the values in the hypothyroid dog started at a lower level than those in the euthyroid animal and reached a value after atropine equivalent to the latter, Balourdas described the response to atropine in the hypothyroid heart as exaggerated. At any rate, these studies in the dog do not support the likelihood of ventricular failure in hypothyroidism.

Although the effects of hyperthyroidism on various biochemical processes have been extensively studied, there are very few data concerning the effects of hypothyroidism at a cellular or subcellular level. Studies of substrate utilization by the heart in hypothyroidism are incomplete. Deitrich and Smith[28] have shown reduction in butyrate oxidation by the myocardium in the hypothyroid rat and, therefore, suggested that such hearts would not support an increased work load. Decreased levels of activity of certain enzymes concerned with the citric acid cycle or the later stages of electron transport and reduced concentrations of adenosine triphosphate and creatine phosphate have been reported in a few studies.[29] However, the coupling of oxidation to phosphorylation appears to be unchanged in mitochondria from hypothyroid animals as compared with those from normal animals.[30] It is difficult to assess the significance of these isolated observations in view of the other experimental evidence of normal response of the hypothyroid heart to increased temperature or work load.

The mechanism by which thyroactive materials stimulate the heart and the adaptive mechanism whereby function is maintained in the absence of thyroid hormone remain obscure. It is known that cardiac responsiveness to epinephrine in profound hypothyroidism is decreased[31] and that the blood pressure and heart rate increase, observed following infusion of epinephrine, is significantly less in myxedema than in the euthyroid man. However, response to infused catechols is normal in the hypothyroid state treated by very small doses of desiccated thyroid which maintain the basal metabolic rate at levels of minus 20 to minus 25 per cent.[31]

Thus, although the presence of dyspnea, orthopnea, edema, cardiomegaly,

nocturia, effusions, and an abnormal electrocardiogram all suggest the presence of heart disease, it appears in summary that congestive heart failure in the precise sense of that term is rare, if it occurs at all, in uncomplicated cases of myxedema. Buttressing this viewpoint are the facts that in hypothyroidism (1) pulmonary congestion is rare, (2) resting pulmonary arterial pressures when measured are normal or slightly elevated, (3) the right ventricular pulse pressure and the end diastolic pressures are normal, (4) peripheral venous pressures are normal, (5) the effusions when studied have a very high protein content in contrast to the low protein content of effusions of congestive failure, (6) the plasma volume is low in contrast to the increased volume in congestive failure, (7) the condition is generally not responsive to digitalis, but on the other hand is specifically reversible by thyroid preparations alone. In addition, the clinical condition is usually distinctive, being characterized by an adynamic picture with lethargy, slow pulse and respiration, sluggish heart action, infrequent cyanosis, rare pulmonary or hepatic congestion, and absence of clinical manifestations of increased venous pressure.

Pericardial Effusion.—Although pericardial effusion was noted in the early descriptions of hypothyroidism, it was not accorded a major pathogenetic role. Several authors, however, have recently emphasized its frequent occurrence and attribute to it a most important role in the genesis of cardiac signs and symptoms. Kern and colleagues[32] in 1948 summarized the 21 published proved cases and criticized the prevailing concept that the effusion was rarely a contributing factor to the increased cardiac silhouette. They added 4 consecutive cases, in which none of the patients displayed any evidence of congestive failure and in which 2 showed relatively little enlargement of the heart shadow by x-ray. One patient showed a reversible accumulation of pericardial fluid and associated ECG changes, with and without thyroid therapy, on two separate occasions. Kern thus suggested that ECG alterations may be due more to fluid accumulation than to any myocardial damage. They noted that 3 patients had evidence of effusions for 4, 5, and 16 years before myxedema was recognized, yet all became well under thyroid therapy without any obvious residual cardiac abnormalities. One patient had as many as 75 pericardial taps during the 16 years before thyroid therapy was finally given. Another patient, at necropsy, had an essentially normal-sized heart with 4,000 ml. of fluid in the pericardial sac. Marks and Roof[33] in 1953 reviewed the 44 reported cases and added 2. They emphasized the excellent response to thyroid therapy as strong evidence against coexisting significant myocardial fibrosis or hypertrophy. It is noteworthy that pulmonary congestion was not found (normal right auricular pressure and peripheral venous pressure as noted before) and that digitalis preparations were of no benefit. Pericardial tamponade has been noted in only one reference.[21] However, a prominent diastolic dip on the right ventricular pressure tracing is suggestive of limitation of diastolic filling. It would thus appear that pericardial effusion plays a frequent and important role in the genesis of certain of the signs associated with myxedema.

Pleural Effusion and Ascites.—In the Commission report in 1888, note was made of one case of ascites in myxedema among the 72 cases reported. Since that time, there have been intermittent reports. Paddock[34] found the ascites

in his case indistinguishable from that resulting from a variety of conditions. On the other hand, Watson, Craig, and Beach[35] noted a positive test for mucin in ascites in their patient, suggesting that the effusions represented an outpouring of mucinous fluid from serous surfaces. Schneierson and Katz[36] reported a case of unilateral pleural effusion as the sole presenting effusion in a case of myxedema. Tatum[37] described pleural, pericardial, and peritoneal effusions in experimental myxedema in rabbits and sheep. Marks and Roof[33] noted that, in 25 cases of pericardial effusion, 13 had an associated pleural or peritoneal effusion or both. It is considered unlikely that the effusions are due to (1) any primary myocardial insufficiency, as they respond so well to thyroid therapy alone, or (2) renal retention for, despite the lowered glomerular filtration rate in myxedema, the capacity to excrete salt and water is normal (see below). More likely explanations may be found in (1) the observations by Lange[38] of a marked increase in capillary permeability in myxedema, returning to normal with therapy, (2) the marked increase in protein content of the effusions, and (3) the demonstration by Watson and Pearce,[39] using histochemical methods, of the interstitial accumulation of hydrophilic polysaccharides in localized myxedema lesions.

Pulmonary Function.—Blumgart[18] found a consistent decrease in vital capacity in myxedema in the absence of any signs of congestive heart failure. Because this decrease was not closely correlated with the decreased basal metabolic rate and did not change significantly following therapy, they concluded that the mechanism was unknown, and that there was no clear relation to the myxedematous state. Wilson and Bedell[40] in a study of myxedematous patients with and without associated obesity, found the vital capacity to be essentially normal in 16 nonobese patients with uncomplicated myxedema. They found further a normal minute volume of respiration and normal arterial carbon dioxide tension and arterial oxygen. However, they did observe a lower minute volume of ventilation following the stimulus of breathing 7.5 per cent carbon dioxide than occurred in normal subjects and postulated a possible depression of the respiratory center or an inability of the chest bellows to respond to the stimulus. They found further a decreased maximal breathing capacity, suggesting a muscular lesion which returned to normal on therapy. They also noted a decreased diffusion of carbon monoxide which improved on therapy and suggested a possible decrease in the number and size of pulmonary capillaries, or a decreased pulmonary capillary blood volume concomitant with the decreased total blood volume or nonspecified changes in the pulmonary capillary vessels. When, however, myxedema was associated with obesity, they noted a moderate decrease in the inspiratory capacity, expiratory reserve volume, vital capacity, residual volume, and the total lung capacity.

Renal Function.—Corcoran and Page[25] found a decreased renal blood flow, glomerular filtration rate, and tubular secretory capacity in myxedema. Beaumont and Robertson[41] noted a decreased urea clearance but no change in renal concentrating ability. In a comparative study of renal function in low output heart failure and myxedema, Davis[42] found that, whereas the glomerular filtration rate, renal blood flow, and cardiac output were low in both conditions, the capacity to excrete ingested salt and water remained normal in myxedema in con-

trast to a marked decrease in congestive failure. Yount and Little[43] in careful clearance studies confirmed the decrease in glomerular filtration rate, renal plasma flow, and renal blood flow but noted that the values for the filtration fraction were quite variable, several being in the normal range.

Electrocardiogram.—The ECG reveals characteristic, but not diagnostic, alterations in myxedema. The most common is a flattening or inversion of the T wave. Means found this alteration in one or more leads in all of 24 reported cases. Lead II was the most frequently involved (23 of 24 cases). Additional findings are abnormal axis deviation, a low electromotive force causing small complexes in several leads, low, flat, or inverted T waves, an occasional increased P-R interval, notched and widened QRS complexes, and occasional conduction disturbances (bundle branch block, premature beats, interventricular block). It is noteworthy that the abnormal T wave pattern may obscure the hypertensive effect until after therapy when the T waves change to the characteristic inversion of T_1 and a higher T_3 of the hypertensive pattern. Characteristically, evidences of hypothyroidism revert to normal following proper replacement therapy. The ECG changes were initially attributed to assumed alterations in the myocardium or to the easier dissipation of the heart current through the myxedematous tissues of the body. However, comparable changes have been produced experimentally by the infusion of saline into the pericardial sac. Furthermore, improvement of the ECG toward normal has been noted on the day of removal of pericardial fluid. Finally, the reversible changes with and without thyroid therapy have been correlated closely with the presence or absence of pericardial fluid. Thus, the present consensus favors the major role of pericardial effusion as contributing to the alterations of the ECG pattern, excluding conduction disturbances.

Angina Pectoris.—Although there has been much discussion of the role of hypothyroidism in predisposing to atherosclerosis, it is noteworthy that angina pectoris is uncommon in cases of myxedema. However, a few cases have been described of angina present during the hypometabolic state, improving or disappearing following thyroid therapy. In 55 cases of myxedema reported from the Mayo Clinic with pre-existing angina, treatment was followed by disappearance of angina in 5 and improvement in 6.[44] It is of practical significance, however, that far more commonly angina pectoris may follow the institution, in hypothyroid subjects, of thyroid replacement therapy which may be given too rapidly or in too large a dose. In the same series from Mayo, 9 patients became worse on replacement therapy and 12 of 35 with myxedema developed angina for the first time within a year of institution of therapy.

The Therapeutic Use of Induced Hypothyroidism in Heart Disease.—On the basis of the concept that the adequacy of blood flow to the tissues could be determined only in relationship to their metabolic needs, Blumgart and others[45] in 1930 considered that "if the normal metabolic rate of the patient with congestive heart failure or angina pectoris was reduced, his blood supply, while not necessarily altered, might nevertheless be sufficient for the lowered needs of the body." The validity of this hypothesis was confirmed by the results obtained in surgical thyroidectomy in over 350 patients with intractable angina pectoris or congestive

heart failure operated upon in 26 different clinics.[46] The magnitude of the operation in this group of critically ill patients, however, precluded general adoption of the procedure. With the development of the thiourea derivatives, efforts at the induction of hypothyroidism by medical means were undertaken.[47-50] While favorable effects were reported by some observers, the inability to induce a hypothyroid state with certainty or to maintain a hypothyroid state for an indefinite period, and the potential hazard of the lifetime administration of such drugs, made their replacement desirable. With the availability of radioactive iodine from the atomic pile in 1947, the use of radiation for the induction of hypothyroidism was reported.[51] The initial favorable results were confirmed in a compilation of results obtained from many cooperating clinics throughout the United States. Our own experience had indicated that two thirds of patients with angina pectoris and more than half of the patients with congestive heart failure would obtain worth-while amelioration of symptoms following the induction of hypothyroidism. In the cooperative series,[52] 78 per cent of the patients with angina pectoris and 68 per cent of those with congestive heart failure obtained worth-while results. These benefits have been confirmed in more than two dozen publications from a variety of clinics. Two particularly large series have been published. Storaasli[53] has treated over 200 patients with good results in 76 per cent of those with angina pectoris and 56 per cent of those with congestive heart failure. Jaffe and Corday[54] have evaluated the results in over 200 patients treated with radioiodine for angina pectoris and demonstrated beneficial results in 80 to 90 per cent of the patients with follow-up for as long as 10 years. The mechanism of action of radioiodine treatment of the euthyroid cardiac patient remains to be completely clarified. In part, the benefit results from reduction of total body metabolism with its accompanying reduction in the circulatory requirements of the heart to within the limit of the cardiac reserve. It may also act by lessening the sensitivity of the heart to local or circulatory catechol amines or by hitherto unrecognized effects on myocardial contractile proteins or enzyme systems.

The susceptibility of the heart in hyperthyroidism to auricular fibrillation, flutter, and other arrhythmias and the disappearance of these arrhythmias upon re-establishment of the euthyroid state are well known. Moreover, many of our euthyroid patients with intractable congestive heart failure have had chronic atrial fibrillation for many years. Following the induction of hypothyroidism, 3 such patients resumed a sinus rhythm which they have maintained for a number of years. A similar experience is reported by Eliasch and associates.[55] This suggested that desirable results might be obtained by the induction of hypothyroidism in euthyroid patients with uncontrolled supraventricular arrhythmias. A small number of such patients who have been treated by us have experienced substantial benefit.[56] A larger series of such patients has been described by Corday and co-workers.[57] Twenty-five euthyroid patients subject to recurrent paroxysmal supraventricular tachycardia resistant to usual therapy were treated with radioiodine. Of these, 20 had a good result, 17 experiencing no further paroxysms, and an additional 3 had only occasional episodes. Three other patients had a fair result and in only 2 were the results considered poor.

In continuing studies in our laboratory,[58] an abnormality has been found in about one half of such patients—an increase in the in vitro red blood cell uptake of I^{131} triiodothyronine from whole blood which we regard as a measure of the distribution of thyroid hormone between the specific binding sites on the plasma proteins and the red cell membrane. In addition, the in vivo rate of turnover of infused I^{131} thyroxine was significantly increased in a group of these patients. A beneficial effect of stable iodine administration in decreasing or abolishing the paroxysms has been observed, correlating with the return of the in vitro uptake to normal.[59] The mechanism of action of radioactive or stable iodine in controlling the arrhythmias remains unknown and is under study in our laboratory.

SUMMARY

An attempt has been made to review, from the large body of pertinent data, certain aspects of cardiovascular structure and function in hypothyroidism. Although significant alterations have been defined, the preponderance of the data indicates that myocardial decompensation is only rarely, if ever, a consequence of hypothyroidism. Furthermore, the widely assumed causative role of the hypothyroid state per se in the pathogenesis of atherosclerosis is questioned and the need for a critical re-evaluation defined, particularly in the less severe cases and in patients without attendant complicating factors such as age, hypertension, diabetes, etc. The important role of pericardial effusion in the genesis of certain signs and symptoms is underlined. The meagerness of data relating to significant biochemical effects of hypothyroidism at a cellular or subcellular level is noted. The lack of significant effects of hypothyroidism on the related pulmonary and renal functions is delineated. The induction of hypothyroidism for the therapy of severe angina pectoris or congestive heart failure is reviewed; the need is underscored for further study of (1) the mechanism of action of lowered thyroid function on these cardiac conditions, (2) the abnormalities of thyroid hormone binding, tissue uptake, and turnover in certain euthyroid patients with supraventricular tachycardias, and (3) the therapy of this condition by antithyroid measures.

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NERVOUS AND MUSCULAR SYSTEMS IN MYXEDEMA

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IN RECENT years, increased emphasis has been placed on the neuromuscular manifestations of myxedema. Indeed, in some patients with this disease, the major and presenting symptoms are related to the nervous and muscular systems[1] (Table I). Major psychoses have long been recognized as an important feature of myxedema.[2] Lately, more profound disturbances of cerebral function, such as coma and convulsions, have been stressed. The presence of a cerebellar syndrome in patients with myxedema has recently been described. There is also evidence that peripheral neuropathy may be found in the disease. Myopathy, occasionally accompanied by a striking myotonia, is observed in some cases. The frequent and often marked elevation of the cerebrospinal fluid protein lends further significance to the presence of neurological abnormality in myxedema.

COMA AND CONVULSIONS

Myxedema is rarely listed in standard textbooks of medicine as a cause of coma or convulsions. The increasing number of case reports[1,3-15] of myxedema coma, especially in the British literature, have attested the importance and gravity of this complication. The condition occurs most often in the seventh decade of life, usually in women with long-standing unrecognized myxedema. In the majority of cases the onset of coma has been during the winter months. This is not surprising since decreasing environmental temperature increases the requirements of the patient for thyroid hormone.[6] The development of coma may progress slowly over a period of days; however, such events as trauma, heart failure, operation, environmental exposure, burns, and infection may rapidly accelerate its rate of progression.[7,8] In approximately 25 per cent of the cases reported, grand mal convulsions have preceded the appearance of coma.[1] Convulsions may occur independently of coma in myxedema and in rare instances have led to neurosurgical investigation.[9] Nickel[10] found 58 patients with hypothyroidism in a study of psychotic and psychoneurotic patients. Forty-nine of these had a basal metabolic rate of minus 20 or lower. Of the 58 patients, 10 had episodes of grand mal seizures.

The mortality rate in myxedema coma is extremely high. In approximately 30 cases reviewed by Nickerson and associates,[26] only 7 patients have survived, giving a death rate of 77 per cent. The clinical appearance of the patient in myxedema coma is quite striking and is similiar to that of an animal in hiber-

TABLE I. NEUROLOGICAL AND MUSCULAR MANIFESTATIONS IN 25 PATIENTS WITH MYXEDEMA

	NO. OF PATIENTS
Paresthesia	25
Diminished peripheral sensation	15
Subjective weakness	25
Objective muscle weakness	7
Deep tendon reflexes:	
Slow relaxation	24
Absent	1
Memory impairment	21
Dysarthria:	
Slurring speech	18
Muscle cramps	14
Mental retardation	14
Myoedema (mounding phenomenon)	6
Ataxia:	
Subjective	17
Objective	5
Positive romberg sign	5
Tinnitus	5
Psychosis	3
Nystagmus	2
Coma	1

nation. The limbs are limp and areflexic and there is a cadaveric coldness to the skin. Rectal temperatures are usually very low, dropping at times to 74°F.[11,12] Respirations are slow and shallow. The heart rate is slow and hypotension is present. Neurological localizing signs are not found in the typical case.

Once coma has developed, it is most often irreversible and in general treatment is unsatisfactory. Angel and Sash[8] analyzed the details of therapy in 3 of their own cases of myxedema coma and in 25 cases from the literature. Summers,[13] after reporting 4 fatal cases, considered that the body did not respond to thyroid hormone at extremely low body temperatures. Angel and Sash, however, in their review found that only 2 of 6 patients who recovered received attempts at external warming. There is probably no harm in gradual external rewarming with electric blankets and heat cradles so long as cutaneous vasodilation does not occur.

A rapidly acting thyroid preparation is the most important feature of therapy. The need for replacement is so urgent that the 8 to 10 days required for the maximal effect of thyroxin may be too long, although it has been used with a successful outcome in several cases. At the present time parenteral triiodothyronine, with its effect on basal metabolism measured in hours, is the thyroid preparation of choice and should be given in doses proportional to the degree of hypothermia.[14] Initially, 100 mg. of triiodothyronine should be given every 12 hours.[15] This is gradually reduced to 50 mg. or lower depending on response in temperature and pulse rate. Caution must be used with this potent

metabolic agent, especially in patients with cardiac insufficiency. Anderson and Hausman[16] reported increasing angina pectoris and a fatal outcome in a patient with impending myxedema coma given 50 mg.

Two thirds of the patients in reported cases of myxedema coma have been treated with corticosteroids.[8] Initial evidence in the literature suggested that adrenocortical function is decreased in primary myxedema.[17,18] Subsequently, normal plasma 17-hydroxycorticosteroid levels and an adequate response to exogenous ACTH were demonstrated.[19] Angel and Sash found that steroid therapy was employed in only 2 of 6 successfully treated cases of myxedema coma and are of the opinion it is not essential for recovery. Adrenal insufficiency does not appear to be a major factor in the treatment of myxedema coma. The recognition of carbon dioxide narcosis[20] and its prompt treatment may improve the present high mortality rate. Oxygen should not be given before effective ventilation is established. A respirator should be used if necessary. In many instances, the patient may have been receiving suboptimal amounts of fluids, carbohydrates, and proteins. Replacement of vitamins, especially the B-complex group, as well as intravenous carbohydrate, should be considered but not pushed to the point of precipitating congestive heart failure. Patients with myxedema are highly sensitive to narcotics, sedatives, and tranquilizers. Mitchell and co-workers[6] reported upon a patient with myxedema psychosis who lapsed into hypothermic coma after an injection of chlorpromazine. Several other studies have indicated that a drop in the basal metabolic rate occurs after the administration of chlorpromazine.[6] An early diagnosis of impending myxedema coma can often be made by detection of a fall in body temperature. MacDonald[14] is of the opinion that hypothermia alone in myxedema should call forth immediate and vigorous replacement therapy to prevent the onset of coma.

At autopsy, the pathologic alterations in the brain in myxedema coma consist of neuronal degeneration and edema.[21,22] Uyematsu[23] found edematous changes in the brain of a patient with myxedema psychosis. He postulated that this edematous substance might be similar to the myxedematous material found in the subcutaneous tissue. Deposition of such a material in the hypothalamus could be a factor in the initiation of the hypothermia that is seen in the disease. Cerebral atherosclerosis aggravated by hypercholesteremia might be expected to play a role in the pathogenesis of neurological symptoms. There is some question, however, as to whether atherosclerosis is actually accelerated in the myxedematous state. Blumgart and co-workers[24] found little evidence of cerebral atherosclerosis in patients with induced myxedema as treatment for angina pectoris.

The marked hypothermia is the end result of the hypothyroid state and most likely not the main cause for coma. Nevertheless, such extreme degrees of hypothermia as are occasionally seen in myxedema coma may be responsible for some of the cerebral depression. Not all cases of coma due to myxedema, however, have been accompanied by hypothermia.[18,24-26] Further neuropathologic studies are needed in fatal myxedema to help correlate abnormal morphology with clinical manifestations.

Certain physiologic studies have been reported that could have a bearing on the clinical manifestations of myxedema coma. In the area of cerebrovascular

dynamics, Scheinberg and associates[27] noted a significant reduction in cerebral blood flow and in cerebral oxygen-glucose consumption. In addition, there was increased resistance to cerebral blood flow. Sensenbach and co-workers[28] were unable to substantiate this reduction in oxygen-glucose consumption or to find a change after treatment. Carbon dioxide narcosis has been related to myxedema coma by Nordqvist[20] and co-workers. Two patients with severe myxedema who lapsed into coma were described. In both instances respirations were poor and the carbon dioxide tension was found to be significantly increased. Decreased ventilation has been mentioned frequently in fatal cases of myxedema coma. The presence of unrecognized carbon dioxide narcosis is a real and serious factor in at least some patients who develop coma from myxedema. In a recent report, 4 out of 5 patients who died of myxedema exhibited an elevated serum carbon dioxide level.[26] A deficiency of thyroid hormone is known to hinder the action of a number of important cerebral enzyme systems.[29] Since the central nervous system is dependent on these enzyme systems for normal metabolic activity, a deficiency will interfere with cerebral function and may be a factor in the pathogenesis of mental retardation, psychosis, and coma.

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CEREBELLAR SYNDROME

Incoordination is a well-known feature of myxedema. It is characterized by a clumsiness of the hands, an ataxic gait, and general unsteadiness. In some cases, these symptoms may be related to the lethargy and psychomotor retardation of the disease. Odin[30] and Uyematsu[23] both reported what they considered true cerebellar manifestations in myxedema which cleared after thyroid therapy. In the latter instance, cerebellar degeneration was noted in a case which came to autopsy. Levin and Daughaday[18] found the Purkinje cells of the cerebellum to be decreased in foci. Soderbergh[31] observed adiadokinesis in several patients with the disease and ascribed his findings to a cerebellar deficit. The present authors have observed one patient with myxedema who exhibited marked ataxia and adiadokinesis. She was initially admitted to the neurology service with a diagnosis of possible cerebellar tumor. Myxedema was confirmed by laboratory studies. There was partial neurological improvement with replacement therapy, but full doses of thyroid could not be given because of the onset of angina pectoris. Jellinek and Kelly[32] have strengthened the evidence for a cerebellar disorder appearing in myxedema in reporting 6 cases in which evidence of cerebellar insufficiency was prominent. In general, there was improvement with thyroid therapy, but one patient was left with appreciable cerebellar deficit. Recovery may well be dependent upon the duration and severity of the myxedema since all cases did not respond to thyroid. Myxedema should be considered in the differential diagnosis of cases with evidence of cerebellar degenerative disease.

CRANIAL NERVES

Most of the cranial nerves have on occasion been implicated in abnormal function in myxedema. Smell, taste, hearing, and visual acuity have been found to be significantly reduced. Tests of hearing have shown both nerve and middle

ear deafness, either separately or in combination.[33,34] An accompanying feature of the hearing loss in some cases has been a disturbing tinnitus. True vertigo has been described in the disease and at times has been severe enough to cause the patient to fall.[23] Blurring of vision has been reported in from 24 to 45 per cent of patients with myxedema.[1] Individual case reports of primary optic atrophy, retrobulbar neuritis, and retinitis with central scotomas[35] have been described, but it appears that these findings were secondary to causes other than myxedema itself. Walsh[36] is of the opinion that there are no neuroophthalmologic signs in myxedema. An atypical facial neuralgia has been reported that could possibly be related to a disturbance of the sensory portion of the fifth cranial nerve.[37] Slurred speech has been noted in a very high percentage of the cases and has been thought to be the result of myxedematous infiltration of the vocal cords and tongue.[38] There is no available evidence to suggest specific impairment of the tenth or twelfth cranial nerves in myxedema. References to involvement of the spinal cord in myxedema have appeared infrequently in the literature.[39] Individual cases of paraplegia and extensor plantar responses have been recorded, but in these instances and associated vascular or degenerative condition of the spinal cord seem more likely as the underlying cause.

PERIPHERAL NEUROPATHY

Numbness of the hands and feet with pricking and tingling are common complaints of most myxedematous patients.[1] Lancinating extremity pain and burning paresthesia have been described by Crevasse and Logue in patients with myxedema.[40] Objective sensory or motor loss was not detected by these authors in any of the patients and the findings were ascribed on clinical grounds to a related peripheral neuropathy. Burning sensations of the hands and feet, in our experience, are present in approximately 10 per cent of the cases and usually accompany the common pricking-tingling type of paresthesia.

Subjective sensory complaints have been found to be out of proportion to objective sensory deficits, a situation similar to that often seen in diabetic neuropathy. Eighty-three to 100 per cent of patients with moderately advanced myxedema in some series[1,41] complained of disturbing paresthesias in the fingers and toes. Of these, approximately one half were found to have objective sensory loss located distally over the extremities. The majority of those with sensory deficit had decreased pain, light touch and vibratory sensation, while a few had only decreased vibratory sensation. Goldblatt[42] implied there is specific impairment of the neurons carrying vibratory impulses, with sparing of the other fibers.

There are sufficient pathologic changes in the peripheral nerves to account for the observed neurological manifestations. Microscopic examination of the lateral femoral cutaneous or sural nerve[41] (Table II) in many cases reveals an edematous infiltration of the endo- and perineurium by a substance, which is metachromatic with aqueous toluidine-blue stain and basophilic with hematoxylin and eosin. It occurs interstitially and spreads many of the nerve fibers apart. There are focal degenerative changes of the myelin sheaths and axis cylinders consisting of axon distortion and poorly delineated and fragmented neuronal borders (Fig. 1).

TABLE II. NEUROPATHOLOGIC CHANGES OBSERVED IN PERIPHERAL NERVES OF PATIENTS WITH MYXEDEMA

1. Axon-cylinder degeneration
2. Myelin sheath changes
3. Interstitial tissue changes (endo- and perineurium)
   - A. Mucoid infiltration
   - B. Metachromasia
   - C. Fibrosis

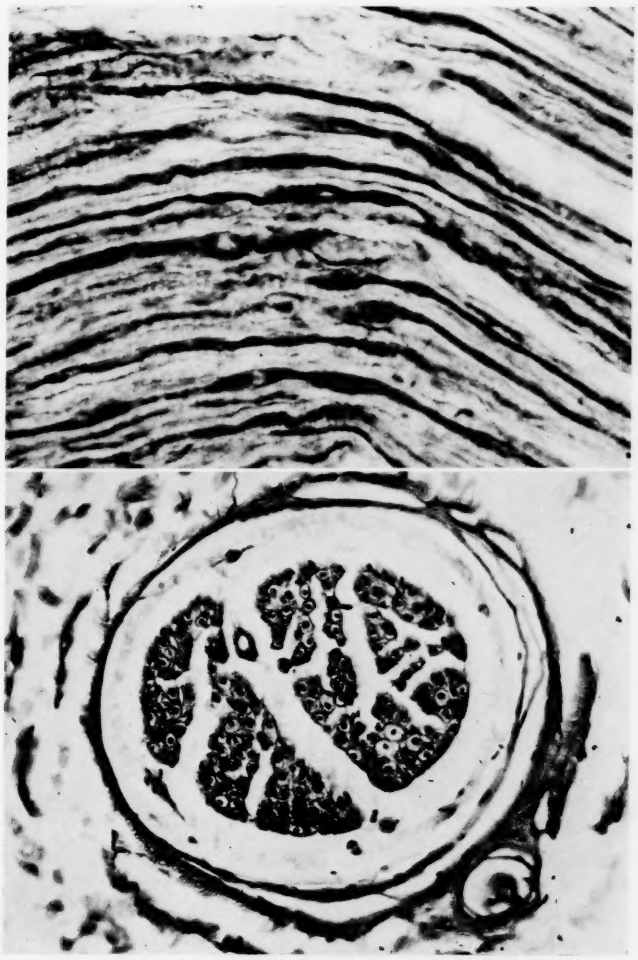

Fig. 1.—*A*, Peripheral nerve of patient with myxedema demonstrating alterations in axis cylinders. (Bodian stain ×720; reduced 2/5.)

B, Small peripheral nerve in cross section, showing marked edema and infiltration of endo- and perineurium by a "mucoid" substance. (Hematoxylin and eosin ×720; reduced 2/5.)

The adverse effect of myxedema on the normal physiologic functioning of peripheral nerves in animals and humans has been observed by a number of investigators. In 1948, Horsten and Boeles[43] noted the influence of hypothyroidism on the conductivity of the sciatic nerve. The optimal frequency of alternating current was lowered and the chronaxie raised 50 per cent in thyroidectomized rats. The change of chronaxie indicated that excitability of the peripheral nerve was reduced. In a more recent study by Murray and Simpson[44] the conduction velocity in the medial and ulnar nerve was determined in 11 myxedematous patients by an electromyographic method. In 3 cases there was delayed conduction through the median nerve from the elbow to the wrist and this was attributed to a carpal-tunnel syndrome. In 4 other patients the conduction time in the median nerve was slightly longer than that in normal subjects, but not significantly so. Murray and Simpson were of the opinion that the paresthesias so common in myxedema were caused by accumulation of edematous tissue under the flexor retinaculum of the wrist, since the paresthesias limited to the thumb and second digit cleared when the retinaculum of one of the patients with typical carpal-tunnel syndrome was cut. Wayne[45] confirmed these studies of carpal-tunnel syndrome and median nerve involvement in 46 of 50 patients with hypothyroidism. This evidence alone is not sufficient to explain the general fading glove- and stockinglike distribution of sensory disturbance in both upper and lower extremities often seen in myxedema. The paresthesias and sensory loss could be caused by a disturbance of sensory corpuscles of the skin or from mechanical interference with the sensory corpuscles by surrounding thickened edematous skin and subcutaneous tissue. Histologic examination of the sensory corpuscles in patients with myxedema would be of interest.

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MYOPATHY

The association of thyroid dysfunction, especially hyperthyroidism, with abnormalities of skeletal muscle, has been noted repeatedly in the past. Periodic paralysis, the myasthenia gravis syndrome, and profound weakness and atrophy of muscles have been observed in patients with hyperthyroidism. The myasthenia gravis syndrome, muscular hypertrophy with myotonia, and muscle weakness have also been noted in myxedema. In a recent study of the neuromuscular aspects of myxedema,[41] all patients complained of subjective weakness. Twenty-eight per cent were found to have objective muscle weakness, primarily of the proximal muscle groups about the shoulder girdle and hips, with sparing of the muscles of the hands and feet. An interesting observation was that of local swelling of directly percussed or pinched muscle (Fig. 2). The terms myoedema and mounding phenomen, have been used in the past to describe this little-mentioned sign. The transient swelling may be so distressing to some patients as to constitute their chief complaint. Muscular aching and spasm are very common, especially in the calves and low back.

From previously reported pathologic studies, it is known that an extracellular "mucinous" substance is present in various tissues of patients with myxedema. Watson and Pearce[46] found that this substance was composed of acid polysaccharides, chondroitin sulfuric and hyaluronic acid, mixed with or

Fig. 2.—Arrow points to myoedema of biceps muscle after percussion with reflex hammer.

in some combination with protein. The most conspicuous and constant finding in muscle has been metachromasia of the sarcoplasm and surrounding connective tissue[41] (Table III). Structural changes in muscle fibers occurred and consisted of cloudiness and granular appearance of the sarcoplasm with loss of striations and myofibrils. These changes were not universal, but confined to certain fibers, particularly the larger ones measuring 90 to 100μ in diameter. There were alterations in the number and position of the sarcolemmal nuclei with displacement to a central position within the fiber. On occasion prominent nucleoli were observed in the nuclei. A striking change noted in some muscle fibers was basophilism of the sarcoplasm, endomysium, and perimysium. In some muscle sections the mucicarmine stain was positive and P.A.S.-positive granules were present in the sarcoplasm (Fig. 3). Lambert and Sayre[47] found histologic abnormalities

TABLE III. HISTOLOGIC CHANGES OBSERVED IN SKELETAL MUSCLES OF PATIENTS WITH MYXEDEMA

1. Architectural changes
   - A. Loss of striations and myofibrils
   - B. Sarcoplasmic degeneration (cloudy, granular, or floccular)
2. Variation in fiber size
   - A. Small (25μ)
   - B. Large (>90μ)
3. Changes in muscle nuclei
   - A. Increased number
   - B. Internally placed
   - C. Large vesicular with prominent nucleoli
4. Basophilic fibers
5. Changes in interstitial tissues (endo- and perimysium)
   - A. Edema
   - B. "Mucoid" degeneration and metachromasia
   - C. Fibrosis

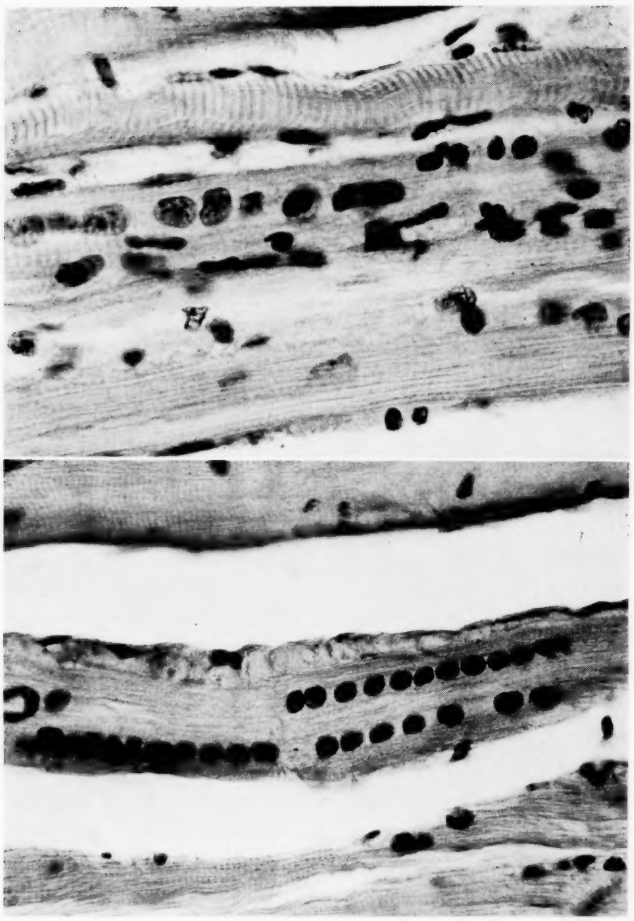

Fig. 3.—*A* and *B*, Muscle fibers with poorly defined cross-striations, chains of internal nuclei with prominent nucleoli, and edema of perimysium. (Hematoxylin and eosin ×940; reduced 2/5.)

in muscle fibers of rabbits following thyroidectomy. The peripheral nerves on the other hand appeared normal to them. The changes in the muscle consisted of vacuolated fibers, various stages of hyaline degeneration, and some evidence of regeneration. The lesions appeared first in the sacrospinalis muscle and, as the condition became more serious, involved the thigh and shoulder-girdle muscles. Fat cells eventually replaced muscle cells and high levels of creatine were noted in the urine. Return of the basal metabolic rate to normal with triiodothyronine is associated with gradually restored muscle structure. Electromyographic examination[48] of muscle in myxedema showed polyphasic action potentials, hyperirritability, repetitive discharge after reflex motion, and low voltage short motor unit potentials.

DEEP TENDON REFLEXES

Although the classic deep tendon reflex in myxedema is striking, the change

is not that usually seen in peripheral neuritis. In the latter, an absence or depression of the reflex without any alteration in the contraction or relaxation phase is observed. On the other hand, the contraction phase of the reflex in myxedema is usually prompt and in most cases active, but with a delayed relaxation phase. The slow rebound reflex is one of the most reliable diagnostic signs in the disease and has been shown to vary directly with the basal metabolic rate in each patient.[49] The diagnostic usefulness is increased by measurement of the half-relaxation phase of the reflex cycle. Both muscular contraction and total relaxation time of the reflex cycle was prolonged in 55 and 65 per cent of the cases, respectively, while more significantly the half-relaxation time was prolonged in 77 per cent.[49] The myxedema reflex was most commonly found in the Achilles tendon, but on occasion it was demonstrated only in the biceps or patellar tendons and not elicited in the Achilles. The myxedema deep tendon reflex most likely represents a fundamental abnormality in the contractile mechanisms of skeletal muscle, but abnormal nerve conduction has not been excluded entirely. There are probably few conditions in which this type of reflex exists. Harrell and Daniel[50] described a man with edema of one arm due to venous and lymphatic obstruction in which the slow rebound deep tendon reflex was noted only in the involved arm. An exception to the characteristic reflex change occurs in myxedema coma, where we have observed complete absence of deep tendon reflexes.

There are certain general features in myxedema, such as sluggishness, fatigue, and psychomotor retardation that suggest involvement of the nervous system. These symptoms are more likely a manifestation of the hypometabolic state affecting all cells of the body. A deficiency of thyroid often gives rise to chronic and recurring headaches.[37] The variety of headache and intensity differ considerably and some patients' headaches show features suggesting migraine. They may manifest as a dull aching or throbbing pain in the temporal, parotid, or occipital area. Joint stiffness similar to the "jelling phenomenon" seen in several of the rheumatic diseases but much shorter in duration occurs in myxedema. Muscle spasm is frequently present in the low back area and also in the calves of the legs.

SPINAL FLUID

The most striking abnormality of the cerebrospinal fluid is the frequent elevation of the protein, occasionally reaching 300 mg. per cent. Seventy-six to 93 per cent of the patients in three series[1,41,51] had an elevated spinal fluid protein. With the administration of thyroid, the cerebrospinal fluid protein returns to normal. Paper electrophoresis of the protein showed an elevation of the gamma globulin similar to that which occurs in the serum of patients with myxedema. The increased spinal fluid protein can be explained on the basis of an alteration in the permeability of the blood-cerebrospinal fluid barrier, which permits protein to enter the spinal fluid by diffusion from serum. The other cerebrospinal fluid protein fractions (albumin, $alpha_1$, $alpha_2$, and beta globulins) separated by paper electrophoresis are not significantly altered in myxedema. A disturbance of the cerebrospinal fluid dynamics, as evidenced by increased spinal fluid pressure from 200 to 430 mm. of water, occasionally occurs.

SUMMARY AND CONCLUSIONS

Profound and disturbing neuromuscular manifestations occur in myxedema and may be the most prominent feature of the disease. Myxedema coma is now more frequently recognized and is a medical emergency requiring the prompt use of rapid-acting parenteral thyroid preparations and proper ventilation to combat carbon dioxide narcosis. Progression of this complication to death can occur in a few hours to days after the onset of coma. Convulsions, psychosis, and cranial nerve involvement are additional features of the advanced hypothyroid state. The cerebellar syndrome which occurs in myxedema is usually but not always improved by replacement therapy. Myxedema neuropathy and myopathy, consisting of paresthesia, sensory loss, and objective muscle weakness, should be added to the list of conditions causing peripheral neuritis and myopathy. A characteristic feature of myxedema is the high gamma globulin and total protein in the cerebrospinal fluid.

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OCCULT HYPOTHYROIDISM AND "METABOLIC INSUFFICIENCY"

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OCCULT hypothyroidism is a diagnosis that has been fraught with speculation and skepticism for many years. In contrast to overt hypothyroidism, where symptoms, signs, and laboratory tests form a characteristic pattern, and where response to replacement therapy is dramatic and consistent, occult hypothyroidism is characterized by relatively vague, nonspecific complaints, few if any clinical signs, normal or equivocal values for many of the customary laboratory tests, and sometimes variable and inconsistent response to therapy. The similarity of the clinical picture to that of psychoneurosis is disturbing to the conscientious physician striving to reach a definitive diagnosis.

In the past 5 years a series of reports claiming the effectiveness of triiodothyronine in the syndrome labeled "metabolic insufficiency"[1-7] has revived interest in this problem, but unfortunately these communications, especially when compared with recent reports of the ineffectiveness of this therapy in double blind placebo studies,[8,9] have increased, rather than dissipated, the confusion existing in this area. It is the purpose of this paper to review the present status of knowledge in this sphere of thyroidology, and point out several aspects that have not been emphasized previously, with the hope that a clearer understanding of what is and is not known will stimulate more definitive and critical investigations in this field.

"METABOLIC INSUFFICIENCY SYNDROME"

Since the introduction of the determination of the basal metabolic rate it has been recognized that some persons have low rates of metabolism without the typical clinical or laboratory picture of hypothyroidism. Many of these persons have no symptoms. Some have a nonthyroidal disorder, such as malnutrition or adrenal insufficiency, that is associated with a lowering of the BMR. When these are excluded, there remain a number with various symptoms, some of which suggest mild hypothyroidism. This condition has been termed "low metabolism without myxedema,"[10] "hypometabolism without myxedema,"[11] "non-myxedematous hypometabolism,"[1,2] "euthyroid hypometabolism,"[7] or "metabolic insufficiency."[3-6]

The unpredictable response to thyroid therapy in such patients has been well known. Kirk and Kvorning[12] reported that only 20 per cent showed objective

improvement and about 35 per cent subjective improvement with desiccated thyroid, the remainder receiving no significant benefit. Freedberg and associates[1,2] emphasized resistance to the administration of desiccated thyroid as an outstanding feature of the syndrome, thus narrowing the original definition, and they suggested that the disorder might result from impairment of the conversion of thyroxine to triiodothyronine in the tissues. Although this interesting speculation has met with much enthusiastic support, up to the present time there has been no proof that such a disorder exists. The first criterion would be the demonstration that patients with the syndrome respond to normal replacement doses of triiodothyronine, but not to desiccated thyroid or thyroxine. Because of differences in the duration of administration of these agents that is required before clinical responses occur, no case reported to date clearly demonstrates resistance to thyroxine in the presence of responsiveness to triiodothyronine. This point will be discussed in more detail later. Furthermore, this hypothesis would imply a deficiency of thyroid hormone activity at the tissue level in the presence of normal thyroid and pituitary function, and it would also imply that the feed-back mechanism that regulates the output of thyrotropin by the pituitary is not dependent upon normal thyroid hormone activity at the cellular level. Neither of these premises has been tested.

The confused status of this disorder is summed up in the following definition taken from advertising literature that has reached the desk of practically every practicing physician in this country: "a condition characterized by clinical symptoms and signs associated with thyroid deficiency, by persistently low or subnormal BMR (when due to subnormal thyroid activity) and, according to current theory, by elevated total serum cholesterol, by *normal* PBI, by *normal* I^{131} uptake and by little or no response to thyroid medications (when due to faulty cellular utilization of thyroid hormone)." The lack of proof of the parenthetic qualifications, which are of prime importance from a physiologic standpoint, and the paucity of reported cases fulfilling all of the criteria listed in the definition are disturbing.

In an attempt to define the syndrome more specifically, Goldberg[7] has recommended other diagnostic criteria that include a normal rise in protein-bound iodine after an injection of thyroid-stimulating hormone and a prolonged electrometric recording of the Achilles tendon reflex. The patients in his series were therefore more precisely chosen than those described in previous reports. Although this study was carefully performed, unfortunately it left several important questions unanswered. It did not include observations of response to thyroxine, which would have been helpful in evaluating the physiologic significance of the resistance to desiccated thyroid. Furthermore, much emphasis was placed on the Achilles tendon reflex as an important criterion for the diagnosis and evaluation of response in "euthyroid hypometabolism," but no mention was made of the possible effects of tranquilizing drugs, which two thirds of the 32 patients in his series "had been taking, or were currently taking," upon this reflex. A case is cited of a patient not included in this series in whom the ingestion of large amounts of tranquilizers apparently inhibited the effect of triiodothyronine in every respect, including the effect on the Achilles tendon reflex, so it would seem

possible, or even likely, that certain tranquilizers might produce a prolongation of this reflex from a previously normal state, or might even produce an iatrogenic "metabolic insufficiency syndrome"! It would therefore be advisable to have subjects discontinue such medications for a sufficient period of time to enable them to return to a base-line state before initiating a study of this type. The time relationship between cessation of tranquilizers and initiation of the studies was not specified. If the sequence of administration of the placebo, desiccated thyroid, and liothyronine had been randomized instead of the same in all cases, possible extraneous factors of this type might have been more readily excluded.

For these reasons, the term, "metabolic insufficiency syndrome," will be employed in this report only for the sake of convenience in referring to cases included under this diagnosis in previous publications, with realization that such a diagnosis has not yet been firmly established on either clinical or physiologic grounds.

OCCULT HYPOTHYROIDISM

This diagnosis, as partly defined in the introductory paragraph of this paper, presents a clinical picture indistinguishable from that of the "metabolic insufficiency syndrome," except that the BMR is not necessarily low. Occult hypothyroidism, however, differs in that the diagnosis can be established by the demonstration of abnormal thyroid function with suitable tests. Sometimes the BMR, PBI, I^{131} uptake, and serum cholesterol level will reveal the abnormality, but if these tests are normal or equivocal, the administration of TSH will demonstrate an inadequate response.

This inadequate response to TSH has been termed "low thyroid reserve,"[13,14] and it appears to be a relatively frequent cause of occult hypothyroidism. It is characterized by a remnant of thyroid tissue that is capable, when functioning at a maximum rate, of sustaining the PBI and I^{131} uptake in the normal range, but is unable to respond to further stimulation. In addition to occurring after subtotal thyroidectomy, where it might be expected, it may be a consequence of partial destruction of the thyroid gland by thyroiditis or I^{131} therapy, or may be encountered as a transient phase in the development of spontaneous myxedema. Its detection is relatively easy through the use of the TSH test,[13-15] provided the patient has not been receiving thyroid medication or iodides. Depending upon various factors, persons with low thyroid reserve may or may not have clinical manifestations. If they possess sufficent residual thyroid function to meet their requirements for thyroid hormone at all times, no signs or symptoms occur. If the residual thyroid function is sufficient to meet their requirements only part of the time, manifestations of thyroid deficiency appear when the demand exceeds the supply. Such patients may complain of symptoms suggestive of hypothyroidism in cold weather, but not during the summer. If the residual thyroid function is inadequate all of the time, even though PBI and I^{131} uptake are within the range of normal, symptoms will be continuous. The diagnosis will obviously be missed if the physician considers a PBI or I^{131} uptake in the normal range to exclude the possibility of abnormal thyroid function. It must be remembered that there is a relatively wide range of normal for these tests, and a level that is

normal for one person under one set of circumstances may not be normal for the same person under different circumstances or for another person. Some patients with low thyroid reserve may therefore have occult hypothyroidism part of the time, some may have it all of the time, and some may not have it at all.

Occult hypothyroidism may also result from other disorders of thyroid function, such as mild defects in ability to form thyroid hormone, either congenital or resulting from exposure to antithyroid agents. In such cases some enlargement of the thyroid gland is usually detectable if a careful examination of the neck is made. The "metabolic insufficiency syndrome," as defined by its sponsors, and if its existence is established, would also be a type of occult hypothyroidism. On the other hand, a review of published reports suggests that many cases classified as "metabolic insufficiency" were actually instances of low thyroid reserve or occult hypothyroidism due to other causes. In the absence of reports of adequate tests of thyroid function, including the TSH test, these possibilities cannot be excluded. Only one investigator[7] has included response to TSH as a test for screening candidates for the diagnosis, and he stated that inadequate response to TSH reduced considerably the number of patients who could be included in the category of the syndrome.

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RESISTANCE TO DESICCATED THYROID

This problem warrants discussion, especially since it has been a major factor in the surge of interest in the "metabolic insufficiency syndrome." Apparent resistance to thyroid medication may result from factors inherent in the preparation itself, or from factors inherent in the subject receiving the medication. Among the former, variation in strength of desiccated thyroid preparations has been a source of confusion to clinicians and patients for many years. Means[16] discusses this problem well, and he emphasizes that adherence to the use of preparations standardized according to U.S.P. specifications should avoid this difficulty. Jackson[17] suggested that variability of response to thyroid medication might result from a loss of potency of thyroid preparations with age, but this phenomenon has not been reported by others and has not been confirmed by pharmacologic studies. The use of enteric-coated thyroid tablets has caused therapeutic difficulties because of variable absorption, so this type of thyroid preparation should be avoided. We have seen several patients with myxedema manifesting irregular, confusing responses to treatment with enteric-coated thyroid tablets whose condition became stabilized nicely when their medication was changed to ordinary, noncoated tablets.

The factors inherent in the patient are more speculative, although no less real. Winkler and his associates[18] first demonstrated that certain patients with persistently low BMR's were resistant to doses of desiccated thyroid as great as 6 grains (0.4 Gm.) daily, yet the BMR responded promptly and briskly to intravenous thyroxine in equivalent amounts. In their series of 24 subjects who manifested relative resistance to desiccated thyroid, no consistent clinical picture characteristic of this phenomenon was observed. Seven subjects had BMR's within the range of normal (above minus 15), and 6 had either a history of or presence of goiter, all except one of the nontoxic variety. The relatively brisk

response to intravenous thyroxine ruled out a defect in utilization of thyroxine at the tissue level and suggested an impairment of absorption of desiccated thyroid as the cause of the resistance.

These investigators also noted a difference in the responses of myxedematous as compared with nonmyxedematous subjects to both desiccated thyroid and intravenous thyroxine, the former being more sensitive to smaller doses and more intolerant of larger ones.[18,19] This suggested a relative resistance to thyroid medication on the part of subjects with intact thyroid glands. Goldsmith and Stanbury[20] observed a more sensitive response of 9 myxedematous subjects to smaller doses of desiccated thyroid, but 8 of these patients tolerated rather large doses before developing signs of toxicity, suggesting a discrepancy between their findings and those of Winkler and his associates in this respect. This discrepancy may be more apparent than real, however, because of differences in duration of treatment in the two studies. Winkler's group employed courses of several months' or even years' duration, whereas Goldsmith and Stanbury raised dosages at 2 week intervals in relatively large increments. Means and Lerman[21] found that doses of 3 grains (0.2 Gm.) daily required as long as 60 days to reach maximum metabolic effect in myxedematous subjects, so Goldsmith and Stanbury's patients might have become toxic at lower levels of thyroid medication if they had been continued for longer periods. Additional studies are therefore necessary in order to clarify the question of difference in sensitivity of myxedematous versus nonmyxedematous subjects to thyroid therapy.

The interest in resistance to desiccated throid received great impetus after the report in 1955 of 4 cases by Kurland, Hamolsky, and Freedberg,[1,2] with the results of trials with sodium-l-thyroxine and sodium liothyronine (sodium-l-triiodothyronine, the more active isomer, as contrasted with d, l-triiodothyronine, a mixture of the 2 isomers[22]). The authors postulated a defect in the conversion of thyroxine to triiodothyronine in the tissues as a possible cause of the resistance to desiccated thyroid, yet when the difference in time required for the achievement of metabolic effects of liothyronine and sodium-l-thyroxine is considered, their data fail to reveal proof that liothyronine was superior to equivalent doses of sodium-l-thyroxine in any patient. It even appears that these patients were relatively resistant to liothyronine as compared with myxedematous subjects. One required 105 mcg. and another 210 mcg. liothyronine (equivalent to approximately 3 and 6 grains of desiccated thyroid, respectively) daily to produce a metabolic response. A third patient showed no significant response to 105 mcg. daily, and the fourth was given liothyronine only in conjunction with sodium-l-thyroxine. Goldberg[7] commented on a similar requirement of relatively large doses of liothyronine necessary to produce improvement in patients with "metabolic insufficiency" in his series. If the difficulty were due to a defect in conversion of thyroxine to triiodothyronine, it would seem more reasonable to expect that smaller doses would be effective.

A more impressive observation made in the cases of Kurland and associates was that combinations of liothyronine and sodium-l-thyroxine appeared to be more effective than either of these agents administered alone. We have observed several definitely hypothyroid patients who seemed to respond better to a com-

bination of these agents than to either alone, so this point should be investigated further.

Four subsequent reports of the dramatic effectiveness of liothyronine in patients with the "metabolic insufficiency syndrome" appeared in the next 2 years.[3-6] The criteria for diagnosis of the syndrome in these communications varied tremendously, and it was difficult to evaluate the high percentage of favorable responses recorded on the basis of the data presented. Nevertheless, there was suggestive evidence that liothyronine was helpful in occasional cases which had not responded to desiccated thyroid in equivalent or larger doses. In these reports only one case was cited that responded to liothyronine after apparently failing to respond to an equivalent or larger dose of sodium-l-thyroxine (Case 1 of Fields[4]), and here the duration of treatment with thyroxine was not specified, so no definite conclusion can be drawn. There have been no further reports, by either these authors or others, of studies of comparative effects of thyroxine and liothyronine in patients with this "syndrome" who were resistant to desiccated thyroid. In one of the reports of double blind placebo studies,[8] the response to desiccated thyroid was not studied and the duration of treatment with thyroxine was inadequate for maximum metabolic effect, and in the other[9] desiccated thyroid was as effective as triiodothyronine when it was administered for a period of 2 months.

Not only do patients without hypothyroidism sometimes show resistance to thyroid medication, but an occasional case of definite hypothyroidism is resistant to desiccated thyroid therapy. Frawley and his associates,[23] in a report of the effects of triiodothyronine in hypothyroidism, describe a case of postoperative thyroid deficiency that failed to respond to doses of desiccated thyroid as great as 12 grains (0.8 Gm.) per day, yet improved dramatically with 50 mcg. d, l-triiodothyronine (equivalent to 25 mcg. liothyronine) daily and maintained improvement on 0.2 mg. sodium-l-thyroxine daily. No BMR's or PBI levels were reported, but the clinical changes were convincing.

We have also encountered a case of hypothyroidism which responded to sodium-l-thyroxine after having become resistant to desiccated thyroid. Because it is the first reported case of this type that has been documented by serial determinations of serum PBI, it is outlined in Table I.

The patient was a 27-year-old medical secretary who had become overweight and chronically fatigued at age 13. Thyroid, 1 grain daily, was administered with symptomatic improvement. A year later the dosage was increased to 2 grains daily. At age 18 the medication was discontinued, but the same symptoms returned, so it was resumed 9 months later, again with improvement. At age 21 the symptoms began to return in spite of the continuation of 2 grains of thyroid daily, so the dosage was doubled. She again felt much better, so this level of therapy was maintained. Five years later, in spite of continuation of treatment, symptoms again returned. Four months subsequently, in February, 1957, a TSH test confirmed the presence of primary hypothyroidism (3 hour I^{131} uptake pre-TSH: 2 per cent; 3 hour I^{131} uptake post-TSH: 2 per cent; 24 hour I^{131} uptake: 1 per cent). The serum PBI while the patient was taking 4 grains of thyroid daily was 4.2 mcg. per 100 ml. Because the desiccated thyroid preparation came from an unknown manufacturer, it was assumed that it was probably weaker than U.S.P. standards, so highly purified and standardized thyroglobulin* in a dosage of 3 grains daily was substituted. A month later the PBI

*Proloid, Warner-Chilcott Laboratories.

TABLE I. HYPOTHYROIDISM RESISTANT TO DESICCATED THYROID, BUT RESPONSIVE TO SODIUM-l-THYROXINE (P.K., 27-YEAR-OLD WOMAN)

DATE	AGE	PBI	THERAPY	REMARKS
1943	13		Desiccated thyroid, 1 grain daily	Chronic fatigue, overweight
1944	14		Desiccated thyroid, 2 grains daily	Asymptomatic
1948	18		Therapy discontinued	Symptoms returned
1949	19		Desiccated thyroid, 2 grains daily	Improved again
1951	21		Desiccated thyroid, 2 grains daily	Symptoms returned on therapy
			Desiccated thyroid, 4 grains daily	Improved again
10/56	26		Desiccated thyroid, 4 grains daily	Symptoms returned on therapy
2/57	27	4.2	Desiccated thyroid, 4 grains daily	TSH test, no response
3/26/57			Proloid, 3 grains daily	
4/26/57		3.1	Proloid, 3 grains daily	
5/3/57			Proloid, 4½ grains daily	
5/28/57		2.6	Proloid, 4½ grains daily	No clinical improvement
6/14/57			Na-l-thyroxine, 0.3 mg. daily	
6/26/57		8.0	Na-l-thyroxine, 0.3 mg. daily	No clinical change
7/5/57		7.6	Na-l-thyroxine, 0.3 mg. daily	Asymptomatic
12/23/57		6.2	Na-l-thyroxine, 0.3 mg. daily	Asymptomatic

was only 3.1 mcg., so the dose was raised to 4½ grains (0.3 Gm.) daily. After a month at this level the serum PBI was 2.6 mcg. and the patient felt no better. The medication was then changed to sodium-l-thyroxine,* 0.3 mg. daily (comparable to approximately 3 grains of desiccated thyroid[23,24]). Twelve days later the PBI had risen to 8.0 mcg., but no subjective change had been noted. Three weeks after the start of thyroxine the PBI was 7.6 mcg. and her symptoms of chronic fatigue and lethargy had disappeared. Six months later, while she was still taking 0.3 mg. daily, the PBI level was 6.2 mcg. and she continued to feel fine.

This case demonstrated several interesting points: After the patient responded initially to normal replacement doses of desiccated thyroid, she developed progressive resistance to this medication. She was also resistant to a more highly purified and standardized preparation of thyroglobulin, but responded nicely to oral sodium-l-thyroxine, the serum PBI level rising before clinical improvement became evident. Over the subsequent 3½ years, there has been no indication of the development of resistance to sodium-l-thyroxine. She moved to another state, so additional PBI determinations could not be obtained. The prompt rise in the PBI level when sodium-l-thyroxine was substituted suggests a defect in absorption of the desiccated thyroid as the cause of the resistance, although it is conceivable that it might have been rapidly inactivated and metabolized after absorption without producing a rise in PBI. Unfortunately, no tests for the presence of antibodies to thyroglobulin were performed. Theoretically, this large molecular substance would be broken down during the process of digestion, however.

Resistance to desiccated thyroid therefore is not confined to a single clinical disorder, but may occur under a variety of circumstances. Responsiveness to thyroxine and triiodothyronine suggests that, in some cases at least, resistance to desiccated thyroid preparations may be related to their animal protein nature in contrast to the synthetic nature of the effective agents. Whether instances of resistance to desiccated thyroid and thyroxine but not to triiodothyronine occur

*Synthroid, Travenol Laboratories.

has not been conclusively proved. Until adequate trials with thyroxine, with respect to both dosage and duration of treatment, are made, this question will remain unanswered.

GONADAL DYSFUNCTION AND INFERTILITY

This is another field in which there is confusion regarding the beneficial effects of thyroid therapy. Although thyroid has been recommended as an empirical treatment in disorders of gonadal function, favorable responses have generally been unpredictable and inconclusive. In the treatment of ovarian dysfunction, critical studies comparing the effectiveness of desiccated thyroid with that of a placebo led to the general conclusion that, in the absence of clinical hypothyroidism, thyroid therapy brought no significant improvement.[25] The observations did not rule out the possibility of benefit from thyroid therapy in an occasional case, however. On the other hand, Foster[26] reported that 95 of 108 women with various types of gynecologic disorders associated with symptoms of hypometabolism responded favorably to the administration of liothyronine. Unfortunately, no tests of thyroid function were performed on these patients, so the number who had hypothyroidism is not known. Sixty-five per cent of the 192 women with symptoms of "hypometabolism" from which this group was drawn were reported to have enlarged thyroid glands, however, so the incidence of thyroid dysfunction was presumably high in this selected series. We have found the incidence of small, nontoxic goiters to be relatively high in patients with ovarian dysfunction and infertility (8 in 42 cases),[27] but, in our experience, more women with ovarian dysfunction have evidence of an abnormality in steroid metabolism than in thyroid function, and cortisone in small doses[27-29] has been more helpful than thyroid. When disorders of ovarian function have been associated with the presence of nontoxic goiters, the combination of cortisone and thyroid therapy has been beneficial after neither agent had been effective alone.

The value of thyroid therapy in women with repeated miscarriages is more clearly established. Peters, Man, and their associates[30,31] have demonstrated that many habitual aborters, although apparently having normal thyroid function in the nonpregnant state, may fail to have a normal rise in serum PBI during pregnancy. When thyroid was administered in doses sufficient to raise the PBI level to the normal range for pregnancy, they ceased to miscarry and their pregnancies continued to term. We have performed TSH tests on several patients of this type in the nonpregnant state and have found the results to be within normal limits, ruling out low thyroid reserve as the cause of this disorder, at least in these patients. It might be a cause in some cases, however. Apparently these women have a defect in the mechanism responsible for the physiologic rise in the PBI during the pregnant state, but the nature of this defect is not yet known. In our experience, the administration of suitable doses of desiccated thyroid or sodium-l-thyroxine has been the most beneficial single therapy in patients with repeated miscarriages. If the PBI is below 6.5 mcg. per 100 ml. during pregnancy in these women, thyroid therapy is routinely started and continued at levels that maintain the PBI above this level. We prefer the longer-acting thyroid

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preparations for this purpose because the PBI may then be used as an index of adequacy of dosage.

Improvements in sperm count and motility in men with oligospermia have been reported with administration of small doses of liothyronine,[32] but the results were not consistent, and in some cases the counts actually decreased with therapy. Tests of thyroid function on these subjects were not reported. Similar results have been observed with administration of desiccated thyroid,[33] so this effect does not seem to be specific for liothyronine. Benefits in some cases of oligospermia with small doses of cortisone or testosterone[28] have also been observed, but the mechanism of these effects is not known.

The interrelationships of thyroid hormone, gonadal hormones, and adrenocortical hormones in gonadal dysfunction and infertility are therefore largely unknown. Estrogen increases thyroxine-binding globulin in plasma[34,35] but whether an abnormality of this action is related to miscarriages has not yet been determined. Triiodothyronine in relatively large doses has been reported to alter androgen metabolism,[36] but whether the effects on ovarian dysfunction or oligospermia are related to this action also remains to be investigated. It has been postulated that the beneficial effects of thyroid medications in gonadal dysfunction result from a nonspecific improvement in cellular metabolism, but this explanation seems unlikely unless a true state of hypothyroidism is present. It is therefore important that disorders of thyroid function be ruled out in subjects undergoing studies in this field.

SUMMARY AND CONCLUSIONS

1. In spite of reports to the contrary, occult hypothyroidism may be difficult to diagnose on the basis of clinical signs and symptoms, and suitable laboratory tests are necessary to confirm the diagnosis. If the BMR, PBI, and I^{131} uptake are normal or equivocal, a TSH test may clarify the nature of the disorder by demonstrating low thyroid reserve. It is conceivable that disorders of thyroid function might occur in the presence of normality of all of these tests, but no such disorder has yet been identified, and the justification for making such a diagnosis remains to be established.

2. Much confusion has been introduced regarding the "metabolic insufficiency syndrome" because of lack of uniformity in criteria for the diagnosis, reflecting a lack of agreement concerning the exact nature of the syndrome, and because of reports of inconclusive studies. The establishment of this syndrome as a specific clinical entity has not yet been accomplished.

3. There are patients who present one of several different clinical pictures, including definite hypothyroidism, and who are resistant to desiccated thyroid, but not to intravenous thyroxine, oral sodium-l-thyroxine, or oral sodium liothyronine.

4. There is suggestive evidence that resistance to desiccated thyroid and sodium-l-thyroxine, but not to sodium liothyronine, may occur, but the existence of this disorder has not been firmly established.

5. In some patients, with or without proved hypothyroidism, the admini-

stration of sodium-l-thyroxine and sodium liothyronine simultaneously may be more effective than either of these agents separately.

6. The effects of thyroid preparations upon ovarian or testicular dysfunction require further study. Evidence for interactions between hormones of the thyroid, the adrenals, and the gonads have been observed, but the nature of these interactions and their relationship to clinical disorders is still largely unknown. Occasional beneficial effects of administration of thyroid preparations upon patients with gonadal dysfunction have been observed, but it is possible that these effects occur only in patients with disorders of thyroid function.

7. The value of thyroid therapy in habitual aborters who fail to have a normal rise in serum PBI during pregnancy is well established, but has apparently not been emphasized to the extent it deserves.

8. More carefully documented and controlled studies in this area of clinical thyroid investigation are greatly needed.

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